



Docket No. 55293-B-PCT-US/JPW/AJM/MVM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Carlos Cordon-Cardo et al.
Serial No.: 10/009,861 Examiner: S. Ungar
Filed : December 10, 2001 Group Art Unit: 1642
For : MARKERS FOR PROSTATE CANCER

1185 Avenue of the Americas
New York, NY 10036

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 C.F.R. §1.132

I, Carlos Cordon-Cardo, hereby declare that:

1. I am one of the coinventors named on the above-identified patent application ("subject application").
2. I am the Director of the Division of Molecular Pathology at Memorial Sloan-Kettering Cancer Center in New York, New York. A copy of my curriculum vitae is annexed as Exhibit 1.
3. The invention described and claimed in the subject application was conceived by Harold I. Scher and me.
4. In accordance with our conception, experiments were conducted either directly by, or under the direction and supervision of, one or both of us.

Applicants: Carlos Cordon-Cardo et al.
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Exhibit A

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5. I understand that the claims pending in the subject application have been rejected by the United States Patent and Trademark Office on the basis of Agus, D.B., H.I. Scher, B. Higgins, W.D. Fox, G. Heller, M. Fazzari, C. Cordon-Cardo and D.W. Golde (1999) "Response of Prostate Cancer to Anti-Her-2/neu Antibody in Androgen-dependent and -independent Human Xenograft Models," *Cancer Research* 59: 4761-4764 (hereinafter "Agus et al.").
6. I am a coauthor of Agus et al., as is my coinventor, Howard I. Scher.
7. At the time the work described in the subject application was performed, D. Agus was a fellow at Memorial Sloan-Kettering Cancer Center located in New York, New York. Under my direction, he performed experimental work relating to the level of Her-2/neu expression in prostate cancer. He did not contribute to the conception of the invention as claimed.
8. At the time the work described in the subject application was performed, B. Higgins was a post-doctoral candidate at Memorial Sloan-Kettering Cancer Center located in New York, New York. Under my direction, he performed experimental work relating to the level of Her-2/neu expression in prostate cancer. He did not contribute to the conception of the invention as claimed.
9. At the time the work described in the subject application

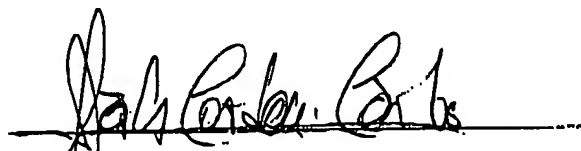
was performed, W.D. Fox was a post-doctoral candidate at Memorial Sloan-Kettering Cancer Center located in New York, New York. Under my direction, he performed experimental work linking cell lines with xenografts and human samples. He did not contribute to the conception of the invention as claimed.

10. At the time the work described in the subject application was performed, G. Heller was a senior statistician in the Department of Epidemiology and Biostatistics at Memorial Sloan-Kettering Cancer Center located in New York, New York. He analyzed the data from the experimental work relating to the claimed invention. He did not contribute to the conception of the invention as claimed.
11. At the time the work described in the subject application was performed, M. Fazzari was a student under the guidance of Dr. Heller at Memorial Sloan-Kettering Cancer Center located in New York, New York. She analyzed the data from the experimental work relating to the claimed invention. She did not contribute to the conception of the invention as claimed.
12. At the time the work described in the subject application was performed, D.W. Golde was the Physician-in-Chief at Memorial Sloan-Kettering Cancer Center located in New York, New York. He assisted me in supervising certain experimental work relating to the claimed invention. He did not contribute to the conception of the invention as claimed.

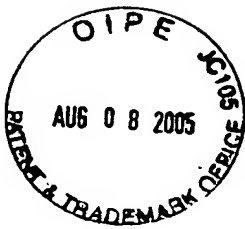
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the subject application or any patent issuing thereon.

Dated: September 2, 2005



Carlos Cordon-Cardo



Carlos Cordon-Cardo, M.D., Ph.D. 1

CURRICULUM VITAE

Name: Carlos Cordon-Cardo, M.D., Ph.D.

Date of Birth: February 25, 1957

Place of Birth: Calella, Barcelona, Spain

Nationality: United States of America

Office Address: Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10021
Tel. #: 212/639-7746
Fax #: 212/794-3186
e-mail: cordon-c@mskcc.org

Home Address: 860 U.N. Plaza, #14F
New York, New York 10017
Tel. #: 212/355-2818
Fax #: 212/355-3447

Education:

1972 - 1975 B.S. - Biology - "Santa Ana" College, Mataro, Spain.

1975 - 1979 Medical Student, Autonomous University of Barcelona, School of Medicine, Barcelona, Spain.

1979 - 1980 Student Exchange Program between U.S. A. and Spain, Senior Clinical Clerkship, New York Medical College, New York.

1980 M.D. - Autonomous University of Barcelona, School of Medicine, Barcelona, Spain.

1981 M.D. License - Madrid, Spain.

1980 - 1982 Ph.D. Student, Experimental Pathology, Department of Pathology, New York Hospital, Cornell University Graduate School of Medical Sciences.

1982 - 1984 Ph.D. Candidate, Cell Biology and Genetics, Memorial Sloan-Kettering Cancer Center, Cornell University Graduate School of Medical Sciences.

1985 Ph.D. - Cornell University Medical College, Graduate School of Medical Sciences, New York. Ph.D. in Cell Biology and Genetics.

Postdoctoral Training:

- 1982 - 1983 Research Fellow, Department of Pathology, Memorial Sloan-Kettering Cancer Center (MSKCC), New York.
- 1983 - 1987 Special Fellow, Immunopathology, Department of Pathology, MSKCC.

Positions and Appointments:

- 1976 - 1979 Instructor, Department of Pathology, Autonomous University of Barcelona, School of Medicine, Barcelona, Spain.
- 1983 - 1987 Research Associate, Cell Biology & Genetics, MSKCC, New York.
- 1987 - 1991 Assistant Attending Immunobiologist, Department of Pathology, and Assistant Member, MSKCC, New York.
- 1988 - Present Head, Laboratory of Molecular Immunopathology, MSKCC, New York.
- 1992 - 1998 Associate Attending Molecular Pathologist, Department of Pathology, and Associate Member, MSKCC, New York.
- 1992 - 1994 Acting Director of Experimental Pathology, Department of Pathology, MSKCC.
- 1992 - Present Associate Professor of Pathology, Cornell University Medical College, New York.
- 1995 - Present Director, Division of Molecular Pathology, Department of Pathology, MSKCC.
- 1998 - Present Attending Molecular Pathologist, Department of Pathology, and Member, MSKCC, New York.
- 2001 - Present Attending Molecular Pathologist, Department of Urology, MSKCC.

Scientific and Medical Societies:

- United States & Canadian Academy of Pathology
- American Society for Investigative Pathology
- American Association for Cancer Research
- American Association for the Advancement of Science
- International Society of Urological Pathology
- Society for Applied Immunohistochemistry
- Association for Molecular Pathology

Scientific and Medical Societies - cont'd

1983 - 1987	Committee on Immunodiagnosis, Union Internationale Contre le Cancer (UICC), Geneva, Switzerland.
1988 – 2000	Urinary Bladder Cancer Marker Network, National Cancer Institute (NCI). Chairman, 1989 - 1992.
1993 - Present	State Legislative Committee of New York, American Association for Cancer Research, Inc. (AACR)
1994 – 1997	Member, Scientific Advisory Committee, "Comite para la Estructuracion del Centro Integral de Oncologia," Spain.
1995 – 2000	Member, Subcommittee C (Basic and Preclinical) of the Cancer Centers and Research Programs Review Committee, National Cancer Institute.
1996 - Present	Member, "Roll of Honour" of the International Union Against Cancer (UICC), Geneva, Switzerland.
1998	Member, Scientific Organizing Committee, 1999 AACR Annual Meeting.
1998 – 1999 1999 – 2000	Chair Elect, Solid Tumors Section, Association for Molecular Pathology Chair, Solid Tumors Section, Association for Molecular Pathology
1998 –2000	Member, WHO Collaborative Project and Consensus Conference Genetic and Molecular Clasification of Urothelial Premalignant and Malignant Lesions
1999	Member, Scientific Organizing Committee, 2000 AACR Annual Meeting.
1999 – 2000	Member, Clinical Research Subcommittee, 2000 AACR Annual Committee; Chairperson, Molecular Biology/Molecular Oncology in the Clinic Section
2000 – 2001	Member, External Scientific Advisory Board, American Health Foundation
2000 – Present	Member, Career Development Awards Committee, AACR
2001 - 2003	Member, Kidney/Bladder Cancers Progress Review Group (Co-Chair Discovery Group), National Cancer Institute

Scientific and Medical Societies - cont'd

- 2003 - Present** Member, Molecular Targets Working Group, National Cancer Institute
- 2003 – Present** International Clinical Proteomics Advisory Committee
- 2004 – Present** Translational Research Initiative - MSKCC
- 2004 – Present** New York Academy of Sciences - Genomic Medicine Discussion Group

Honors and Awards:

- 1985** Academic Achievement - Graduate School of Medical Sciences
Cornell University Medical College, New York, May 1985
- 1986** Catedratico Auxiliar "Ad Honorem," Universidad Central del Caribe
School of Medicine, Puerto Rico
- 1989** The American Academy of Pediatrics, Honorable Mention Award -
Urology Section, October 1989
- 1991** Louise and Alliston Boyer Young Investigator Award,
Memorial Sloan-Kettering Cancer Center, New York, May 1991
- 1994** Paul Harris Award - Rotary International, Barcelona, December 1994.
- 1995** Jaime Esperalba Award - Academia de Ciencias Mediques de Catalunya i
Balears, June 1995
- 1995** Annual Scientific Award - Academia Medico-Quirurgica Espanola.
"Academico de Numero" - Madrid, December 1995
- 1996** "Roll of Honour" - International Union Against Cancer (UICC),
Geneva, Switzerland
- 1996** "C.G. Ahlstrom Lecture" and "Medal of the Swedish Society of
Physicians" - Stockholm, Sweden, November 1996
- 1998** Marquis Who's Who in America – Annual Member Biographee
- 1999** The Ramon y Cajal Lectures. The Spanish Institute, New York, February 1999
- 2000** "Don Santiago Ramon y Cajal Memorial Lecture," Spanish American Medical
and Dental Society, New York, October 2000

Honors and Awards - cont'd

- 2002 "Strathmore's Who's Who – Lifetime Member"
- 2002 "Premio Europa 2002," La Rebotica, Madrid, Spain, June 2002
- 2002 "American Registry of Outstanding Professionals – Lifetime Member"
- 2003 President, Scientific Committee "I Salon Internacional de la Salud," Santiago de Compostela, Spain, March 2003
- 2003 "Key Note Lecture," 2nd International Conference on Translational Research and Pre-Clinical Strategies in Radiation Oncology, Lugano, Switzerland, March 2003
- 2003 Honorary Member, "Spanish American Medical and Dental Society. Delivered the "Don Santiago Ramon y Cajal Memorial Lecture," Spanish American Medical and Dental Society, New York, October 2003
- 2003 Member, Board of Directors, Queen Sofia Spanish Institute, New York, September 2003
- 2003 "16th Burchenal Lecture," 28th Annual Alumni Society Meeting, Memorial Sloan-Kettering, New York, November 2003
- 2004 "Key Note Lecture," Winter Meeting, Finnish Urological Association, Helsinki, Finland, February 2004
- 2004 "Key Note Lecture," XIV EuroCellPath, Girona, Spain, May 2004
- 2004 Gold Medal – Scientific Merit, 125th Anniversary "Correo Gallego," Spain
- 2004 "Highly Cited Researcher – Clinical Medicine Category," Institute of Scientific Information (ISI) (<http://www.isihighlycited.com>)
- 2004 Gold Medal – Medical Sciences, Gobierno de Galicia, Spain

Active Grants and Other Awards:

NCI CA 47179 - Program Project Soft Tissue Sarcomas
(PI: M. Brennan, MSKCC) 88/06/01 - 04/06/30 Total Cost \$14,270,978
Project #2: Functional and Immunophenotypic Analysis of p53 and RB Pathways in Adult Soft
Tissue Sarcoma. (PI: C. Cordon-Cardo) Direct Cost: \$159,577 per year
Core B: Pathology. (PI: C. Antonescu; Co-PI: C. Cordon-Cardo) \$61,520 per year

Active Grants and Other Awards – cont'd

NIH/NCI - P01 CA87497 - Roles and Regulation of p53.

(PI: C. Prives, Columbia University) 01/07/01 - 06/06/30 Total Cost: \$10,790,592

Project #5: Molecular and Functional Studies of p53 in Human Cancer.

(PI: C. Cordon-Cardo) Direct Cost: \$204,295 per year

Core B: Histology and molecular pathology.

(PI: C. Cordon-Cardo; Co-PI: W. Gerald) Direct Cost: \$152,669 per year

NIH/NCI SPORE 92629 - SPORE in Prostate Cancer.

(PI: P. Scardino) 01/06/01 – 06/05/31 Total Cost: \$14,468,320

(C. Cordon-Cardo – Scientific Director)

Project #2: Molecular Analysis of Carcinogenesis in the Mouse and Human Prostate.

(PIs: PP Pandolfi and C Cordon-Cardo) Direct Cost: \$219,127 per year

Pathology Core. PI: V. Reuter; Co-PIs: C. Cordon-Cardo, W. Gerald) \$115,500 per year

NIH DK 47650 - George M. O'Brien Urology Research Center-

(PI: W. Heston) 93/09/30 - 03/08/31 Total Cost \$9,241,104

Project #1: Cyclin Dependent Kinase Inhibitors in Benign and Malignant Prostatic Diseases

(PI: C. Cordon-Cardo) Direct Cost: \$84,520 per year

NHI P50 – Imaging Progression and Response in Prostate Cancer.

(PI: S. Larson) 00/03/01 – 05/02/28 Total Cost \$680,020

Specialized Resource in Molecular Pathology – PI: C. Cordon-Cardo

NIH/NCI - P30 CA08748-27

(PI: H. Varmus) 12/31/03-1/1/08 Total Cost \$10,525,500

Cancer Center Support Grant.

Co-Principal Investigator - Cancer Biology and Experimental Pathology Program

Role: Co-Investigator

NIH K08 AR 02129 - Alterations of Cell Cycle Control in Melanocytic Lesions.

PI: D. Polsky - Sponsor: C. Cordon-Cardo 07/01/99 – 06/30/04 Total Cost \$523,400

NIH K08 CA78611 - Clinical Relevance of Circulating Prostatic Tumor Cells

PI: R. Ghossein - Sponsor: C. Cordon-Cardo 07/01/98 – 06/30/03 Total Cost \$411,665

AUA-AFUD MD0010 – Role of Kinase Inhibition in Cell Cycle and Prostate Cancer.

PI: T. Kopie – Sponsor: C. Cordon-Cardo 07/01/04 – 06/30/06 Total Cost \$515,000

Training Program in Molecular Oncology – MSKCC and CNIO (Madrid, Spain)

Fundacion Caja Madrid – Fellowship Program 01/00 – 12/03 Total Cost \$217,500

PIs: M. Barbacid (CNIO)/C. Cordon-Cardo (MSKCC)

Past Research Support:

NCI CM 87215 - Phase I Clinical Trials of Biological Response Modifiers.

Co-Principal Investigator

NCI CA 18856 - Program Project Experimental Therapeutics in Cancer - Project #6.

Co-Principal Investigator 90/01/01 - 94/12/31 Total Cost \$10,533,157

NCI ROI CA 57458 - Combined Modality Approach for Prostate Cancer.

Co-Principal Investigator 92/07/01 - 95/06/30 Total Cost \$491,681

NCI R01 CA 58514 - Bladder Cancer Chemoprevention for HPR - Molecular Approach

Co-Principal Investigator 92/08/01 - 97/07/31 Total Cost \$786,718

NCI-NIEHS R01 CA 61155 - Molecular Epidemiology of Bladder Cancer.

Co-Principal Investigator 93/09/01 - 96/08/31 Total Cost \$587,829

NCI CA 33049 - Monoclonal Antibodies and Vaccines in Cancer Therapy.

Co-Principal Investigator 88/06/01 - 96/05/30 Total Cost \$3,191,814

NIH - T32 CA60376 - Molecular Pathology and Immunobiology of Human Cancer.

(PI: J. Rosai; Co-PI: C. Cordon-Cardo) 94/07/01 – 99/06/30 Total Funds: \$581,000

NCI CA 47538 - Cell Cycle Regulators as Tumor Markers in Bladder Cancer.

Principal Investigator 88/04/01 - 00/03/31 Total Cost \$2,720,688

NCI R01 CA 78497 - DNA-PK in Radiation-Repair and Lymphomagenesis.

Co-Principal Investigator 98/07/01 - 02/06/30 Total Cost \$925,560

AUA-AFUD MD0010 – Role of Kinase Inhibition in Cell Cycle and Prostate Cancer.

PI: K. Pohar – Sponsor: C. Cordon-Cardo 07/01/00 – 06/30/02 Total Cost \$105,000

LLS 3956 The Leukemia & Lymphoma Society – Regulation/Function of p63 and p73: Relatives of The Tumor Suppressor p53

PI: C. DiComo – Sponsor: C. Cordon-Cardo 07/01/00 – 06/01/03 Total Cost \$135,000

Other Activities - Editorial Boards:

- Diagnostic Molecular Pathology
- Journal of Histochemistry and Cytochemistry
- British Journal of Urology (Spanish Edition)
- Clinical Proteomics
- Preventive Medicine
- Applied Immunohistochemistry & Molecular Morphology
- Urologic Oncology
- Molecular Urology

Other Activities - Editorial Boards (cont')

- Critical Reviews in Clinical Laboratory Sciences
- Signal
- Journal of Clinical and Experimental Cancer Research

Past Editorial Boards: Oncologia (97-99), American Journal of Clinical Pathology (98-99), International Journal of Cancer (Pred Oncol) (97-01), Cancer Research (00-02), Clinical Cancer Research (99-02), The American Journal of Pathology (93-03)

Disclosure of Patents (12/01) - Inventor/Co-Inventor: Carlos Cordon-Cardo, M.D., Ph.D.

Application Number:

Title of Disclosure

A. Issued:

567,066	Monoclonal Antibodies to Human Bladder and Ureter Cancers and Method
083,723	Monoclonal Antibodies to Human Lung Cancers and Method
474,415	Monoclonal Antibodies to Human Gastrointestinal Cancers and Hybridoma Method of Production of the Monoclonal Antibodies
474,224	Monoclonal Antibodies to Human Renal Cancer Antigens and Method
562,465	Monoclonal Antibodies to Ovarian and Uterine Human Cancers and Method of Diagnosis
853,730	Monoclonal Antibodies to Human Ovarian Cancers
837,531	Method for Characterizing Types of Renal Carcinoma and Prognosis
604,080	Monoclonal Antibodies to Cell Surface Antigens of Human Teratocarcinomas
718,162	Choriocarcinoma Monoclonal Antibodies and Antibody Panels
449,318	Monoclonal Antibodies to Human Gastrointestinal Cancers

U.S. Serial #/U.S. Patent:

330,591

Title of Disclosure - cont'd

Blood Group Antigen Panel

835,953

Method of Determining Blood Group Antigen Expression on Cells

456,240

Monoclonal Antibodies Specific for Differentiation Antigens Associated with Pigmented Cells

139,654

Cell Surface Antigens of Human Melanocytes and Melanoma: Expression of Adenosine Deaminase Binding Protein is Extinguished with Melanocyte

362,590

Methods for Detecting Pre-Cancerous Cells Using p90 Antibodies or Probes

09/343,634

Ku 70: A Candidate Tumor Suppressor Gene for Murine and Human Cancer

6,780,636

Cryoarray System and Uses Thereof

B. Pending:

PCT/US98/25483

p27 and Prostate Hyperplasia and Prostate Carcinoma Overexpression of G1 Cyclins is Related to Progression in Prostate Cancer

Languages:

Spoken: English, Spanish, Catalan, French

Written: English, Spanish, Catalan

Social Security:

130-66-5634

Marital Status:

Married

Spouse's Name: Alicia Bouzan-Cordon

Dependents:

Two children (Carolina, 03/24/93; and Daniel, 09/19/00)

BIBLIOGRAPHY

PEER-REVIEWED ARTICLES

1. Razin E, Cordon-Cardo C, Good RA: Growth of a pure population of mouse mast cells "in vitro" with conditioned medium derived from concanavalin A-stimulated splenocytes. *Proc Natl Acad Sci USA* 78: 2559-2561, 1981.
2. Razin E, Rifkin AB, Cordon-Cardo C, Good RA: Selective growth of a pure population of human basophil cells "in vitro." *Proc Natl Acad Sci USA* 78: 5793-5796, 1981.
3. Razin E, Cordon-Cardo C, Minick CR, Good RA: Studies on the exocytosis of cultured mast cells derived from mouse bone marrow. *Exp Hematol* 10: 524-532, 1982.
4. Fradet Y, Cordon-Cardo C, Thomson T, Daly ME, Whitmore WF, Lloyd KO, Melamed MR, Old LJ: Cell surface antigens of human bladder cancer defined by mouse monoclonal antibodies. *Proc Natl Acad Sci USA* 81: 224-228, 1984.
5. Mattes MJ, Cordon-Cardo C, Lewis JL, Old LJ, Lloyd KO: Cell surface antigens of human ovarian and endometrial carcinoma defined by mouse monoclonal antibodies. *Proc Natl Acad Sci USA* 81:568-572, 1984.
6. Graus F, Cordon-Cardo C, Posner JB: Neuron-specific antinuclear antibody in a patient with oat cell of the lung and subacute sensory neuropathy. *Neurology* 34 (suppl 1): 1986, 1984.
7. Cordon-Cardo C, Bander NH, Fradet Y, Finstad CL, Whitmore WF, Lloyd KO, Oettgen HF, Melamed MR, Old LJ: Immunoanatomic dissection of the human urinary tract by monoclonal antibodies. *J Histochem Cytochem* 32: 1035-1040, 1984.
8. Graus F, Cordon-Cardo C, Cho ES, Posner JB: Opsoclonus and oat cell carcinoma of the lung. *Lancet* 1 (8392): 1479, 1984.
9. Graus F, Cordon-Cardo C, Houghton AN, Melamed MR, Old LJ: Distribution of the ganglioside GD3 in the human nervous system detected by R24 mouse monoclonal antibody. *Brain Res* 324: 190-194, 1984.
10. Erlandson RA, Cordon-Cardo C, Higgins PJ: Histogenesis of benign pleomorphic adenoma (mixed tumor) of the major salivary glands. An ultrastructural and immunohistochemical study. *Am J Surg Pathol* 8: 803-820, 1984.
11. Felt C, Bartal AH, Fass B, Bushkin Y, Cordon-Cardo C, Hirshaut Y: Monoclonal antibodies to human sarcoma and connective tissue differentiation antigens. *Cancer Res* 44: 5752-5756, 1984.

12. Bander NH, Cordon-Cardo C, Finstad CL, Whitmore WF, Vaughan ED, Oettgen HF, Melamed MR, Old LJ: Immunohistologic dissection of the human kidney using monoclonal antibodies. *J Urol* 133: 502-505, 1985.
13. Rettig WJ, Cordon-Cardo C, Ng J, Oettgen HF, Old LJ, Lloyd KO: High molecular weight glycoproteins of human teratocarcinoma defined by monoclonal antibodies to carbohydrates determinates. *Cancer Res* 45: 815-821, 1985.
14. Houghton AN, Minizer D, Cordon-Cardo C, Welt S, Fleigel B, Vadhan S, Carswell E, Melamed MR, Oettgen HF, Old LJ: Mouse monoclonal antibody detecting GD3 ganglioside: A phase I trial in patients with malignant melanoma. *Proc Natl Acad Sci USA* 82: 1242-1246, 1985.
15. Graus F, Cordon-Cardo C, Posner JP: Subacute sensory neuropathy and small cell carcinoma of the lung: Antibody highly restricted to nuclei of neurons in the serum of two patients. *Neurology* 35: 538-543, 1985.
16. Rettig WJ, Cordon-Cardo C, Koulos JP, Lewis JL, Oettgen HF, Old L.J: Cell surface antigens of human trophoblast and choriocarcinoma defined by monoclonal antibodies. *Int J Cancer* 35: 469-475, 1985.
17. Finstad CL, Cordon-Cardo C, Bander NH, Whitmore WF, Melamed MR, Old LJ: Specificity analysis of mouse monoclonal antibodies defining cell surface antigens of human renal cancer. *Proc Natl Acad Sci USA* 82: 2955-2959, 1985.
18. Cordon-Cardo C, Mattes MJ, Lewis JL, Melamed MR, Old LJ, Lloyd KO: Immunopathology of ovarian carcinoma associated antigens detected by monoclonal antibodies. *Int J Obs Gynecol* 4: 121-130, 1985.
19. Real FX, Houghton AN, Albino AP, Cordon-Cardo C, Melamed MR, Oettgen HF, Old LJ: Surface antigens of melanomas and melanocytes defined by mouse monoclonal antibodies: Specificity analysis and comparison of antigen expression in cultured cells and tissues. *Cancer Res* 45: 4401-4411, 1985.
20. Huffman JL, Fradet Y, Cordon-Cardo C, Herr HW, Pinsky CM, Oettgen HF, Old LJ, Whitmore WF, Melamed MR: Intravesical administration of BCG alters detection of a urothelial differentiation antigen in exfoliated cells of carcinoma in situ of the human urinary bladder. *Cancer Res* 45: 5201-5204, 1985.
21. Graus F, Cordon-Cardo C, Bonfa E, Elkon KB: Immunohistochemical localization of Ro and La antigens in brain: Selective concentration of the La protein in neuronal nucleoli. *J Neuroimmunol* 9: 307-319, 1985.

22. Jaeckle KA, Graus F, Cordon-Cardo C, Houghton AN, Nielsen SL, Posner JB: Autoimmune response of patients with paraneoplastic cerebellar degeneration to a Purkinje cell cytoplasmic protein antigen. *Ann Neurol* 18: 592-600, 1985.
23. Graus F, Elkon KB, Cordon-Cardo C, Posner JB: Sensory neuronopathy and small cell lung cancer: An antineuronal antibody that also reacts with the tumor. *Am J Med* 80: 45-52, 1986.
24. Houghton AN, Cordon-Cardo C: Antigens of melanocytes and melanoma. *Internat Rev Exp Pathol* 28: 217-247, 1986.
25. Sakamoto J, Furukawa K, Cordon-Cardo C, Yin BWT, Rettig WJ, Oettgen HF, Old LJ, Lloyd KO: Expression of Lewis^a, Lewis, X, and Y blood group antigens in human colonic tumors and normal tissue and in human tumor-derived cell lines. *Cancer Res* 46: 1553-1561, 1986.
26. Bartal AH, Cordon-Cardo C, Lichtig C, Felt CF, Robinson E, Hirshaut Y: Murine monoclonal antibody recognizing fetal fibroblasts and a subset of fibroblasts associated with human neoplasms. *J Natl Cancer Inst* 76: 415-421, 1986.
27. Cordon-Cardo C, Lloyd KO, Sakamoto J, McGroarty ME, Old LJ, Melamed MR: Immunohistological expression of blood group antigens in the normal human gastrointestinal tract and colonic carcinoma. *Int J Cancer* 37: 667-678, 1986.
28. Tolkoff-Rubin NE, Cosimi AB, Russel RE, Thompson DJ, Hansen WP, Bander NL, Finstad CL, Cordon-Cardo C, Klotz LH, Old LJ, Rubin RH: Diagnosis of transplant rejection and cyclosporin toxicity by urinary assay for a proximal tubular antigen, the adenosine deaminase binding protein. *Transplantation* 41: 593-597, 1986.
29. Pumarola-Sune T, Graus F, Cordon-Cardo C, Evans RL: A monoclonal antibody that induces T lymphocytes to aggregate reacts with vascular endothelial cells. *J Immunol* 137: 826-829, 1986.
30. Fradet Y, Cordon-Cardo C, Whitmore WF, Melamed MR, Old LJ: Cell surface antigens of human bladder tumors: Definition of tumor subsets by monoclonal antibodies and correlation with growth characteristics. *Cancer Res* 46: 5183-5188, 1986.
31. Cordon-Cardo C, Lloyd KO, Finstad CL, McGroarty ME, Reuter VE, Bander NH, Old LJ, Melamed MR: Immunoanatomic distribution of blood group antigens in the urinary tract. *Lab Invest* 55: 444-454, 1986.
32. Tolkoff-Rubin NE, Cosimi AB, Delmonico FL, Russell PS, Thompson RE, Piper DJ, Hansen WP, Bander NH, Finstad CL, Cordon-Cardo C, Klotz LH, Old LJ, Rubin RH: Monitoring of renal proximal tubular injury in transplantation with a monoclonal antibody-based assay for the adenosine deaminase-binding protein. *Transplant Proc* 18: 716-718, 1986.

33. Furth ME, Aldrich TH, Cordon-Cardo C: Expression of ras proto-oncogene proteins in normal human tissues. *Oncogene* 1: 47-58, 1987.
34. Cordon-Cardo C, Finstad CL, Bander NH, Old LJ, Melamed MR: Immunoanatomic distribution of cytostructural antigens in the human urinary tract. *Am J Pathol* 126: 269-274, 1987.
35. Houghton AN, Real FX, Davis LJ, Cordon-Cardo C, Old LJ: Differentiation of melanoma: Implications for tumor heterogeneity. *J Exp Med* 164:812-829, 1987.
36. Pumarola-Sune T, Navia BA, Cordon-Cardo C, Cho ES, Price RW: HIV antigen in the brains of the patients with the AIDS dementia complex. *Ann Neurol* 21: 490-496, 1987.
37. Welte K, Miller G, Chapman P, Natoli E, Kunicka JE, Cordon-Cardo C, Old LJ, Houghton AN: Stimulation of T lymphocyte proliferation by monoclonal antibodies against GD3 ganglioside. *J Immunol* 139: 1763-1771, 1987.
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MANUSCRIPTS SUBMITTED FOR PUBLICATION

1. Polsky D, Mastorides S, Leung D, Dudas M, Woodruff JM, Brennan MF, Cordon-Cardo C: Two distinct patterns of RB expression correlate with decreased survival of patients with adult soft tissue sarcoma. Submitted for publication.
2. Berwick M, Matullo G, Song YS, Dominguez G, Guarrera S, Cordon-Cardo, Orlow I, Vineis P: Association between Ahr genotype and survival in soft tissue sarcoma. Submitted for Publication.
3. Lu ML, Juan G, Di Como CJ, Drobnjak M, Charytonowicz E, Ahn J, Zhang Z-F, Prives C, Cordon-Cardo C: Chk2 alterations in bladder cancer: Mutagenesis and functional analyses. Submitted for Publication.
4. Segal NH, Qin J, Antonescu CR, Pavlidis P, Woodruff JR, Brennan MF, Houghton AN, Cordon-Cardo C: Genomic characterization of malignant peripheral nerve sheath tumors: a comparative study with schwannoma, soft tissue sarcoma, and melanoma. Submitted for Publication.
5. Sanchez-Carbayo M, Socci ND, Lozano JJ, Haab BB, Cordon-Cardo C: Bladder cancer targeted antibody arrays for serum-based classification of patients with uroepithelial tumors. Submitted for Publication.
6. Cao W, Cai L, Rao J-Y, Pantuck A, Lu M-L, Dalbagni G, Reuter V, Scher H, Cordon-Cardo C, Belldegrun A, Zhang Z-F: Tobacco Smoking, *GSTP1* Polymorphism and Bladder Cancer. Submitted for Publication.
7. Capodieci P, Donovan M, Buchinsky H, Jeffers Y, Cordon-Cardo C, Gerald W, Edelson J, Shenoy SM, Singer RH: Diagnostic Histopathology Using Multiplex Gene Expression FISH. Submitted for Publication.
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11. Forster TH, Drobnjak M, Puig P, Lu M-L, Scardino PT, Cordon-Cardo C: Prognostic significance of Pten in bladder cancer and its cooperative effects with Akt and p53. Submitted for Publication.

REVIEW ARTICLES AND EDITORIAL COMMENTS

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92. Strohmeyer T, Reissman P, Cordon-Cardo C, Hartmann M, Ackermann R, Slamon DJ. Expression of the retinoblastoma tumor suppressor gene is absent or decreased in human malignant testicular germ cell tumors. American Association for Cancer Research, Houston, Texas, May, 1991.
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99. Nanus DM, Lee AC, Motzer RJ, Vlamis V, Cordon-Cardo C, Albino AP, Reuter VE: Expression of basic fibroblast growth factor in primary human renal tumors: Correlation to poor survival. Proceedings 83rd Annual Meeting of the American Association for Cancer Research, San Diego, CA, May, 1992.
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101. Grant SC, Pisters KMW, Divgi C, Kris MG, Cordon-Cardo C, Yeh SDJ, Walsh CM, Heelan RT, Oettgen HF: Phase I trial of RG 83852, an anti-epidermal growth factor (EGF) receptor monoclonal antibody (MAb) in non-small cell lung cancer (NSCLC). Proceedings 83rd Annual Meeting of the American Association for Cancer Research, San Diego, CA, May, 1992.
102. Dalbagni G, Russo P, Fair WR, Wissel P, Cordon-Cardo C: Immunolocalization of epidermal growth factor receptor in normal and malignant urothelium. Proceedings 83rd Annual Meeting of the American Association for Cancer Research, San Diego, CA, May, 1992.
103. Cordon-Cardo C, O'Brien J, Lee A, Finstad C, Vaia V, Motzer R, Reuter V: Pglycoprotein (Pgp) Expression during fetal kidney development: A model of Pgp expression in renal cell carcinomas. Proceedings 83rd Annual Meeting of the American Association for Cancer Research, San Diego, CA, May, 1992.

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105. Aprikian A, Fair WR, Cordon-Cardo C, Reuter V: Primary, metastatic and hormone treated prostatic carcinomas contain a small population of neuroendocrine (NE cells). Proceedings 83rd Annual Meeting of the American Association for Cancer Research, San Diego, CA, May, 1992.
106. Dalbagni G, Presti JC, Reuter VE, Fair WR, Cordon-Cardo C: p53 and chromosome 17 abnormalities in human bladder tumors. Proceedings 83rd Annual Meeting of the American Association for Cancer Research, San Diego, CA, May, 1992.
107. Presti JC, Cordon-Cardo C, Jhanwar SC, Fair WR, Reuter VE: Clinicopathological correlations of molecular genetic alterations in renal tumors. Meeting of the American Association for Cancer Research, San Diego, CA, May, 1992.
108. Drobnjak M, Cote R, Saad A, Drudis T, Cordon-Cardo C: p53 and RB expression in breast cancer: Correlations with hormone receptor and lymph node status. Meeting of the American Association for Cancer Research, San Diego, CA, May, 1992.
109. Presti JC Jr, Reuter VE, Cordon-Cardo C, Thaler HT, Fair WR, Jhanwar SC: Molecular genetic alterations in renal tumors -clinicopathological correlations. AUA 87th Annual Meeting, Washington, D.C., May, 1992.
110. Presti JC Jr, Nanus DM, Cordon-Cardo C, Thaler HT, Albino AP, Lee AC, Jhanwar SC, Fair WR, Reuter VE: Altered expression of the retinoblastoma gene product in renal tumors. AUA 87th Annual Meeting, Washington, D.C., May, 1992.
111. Aprikian A, Fair WR, Cordon-Cardo C, Reuter VE: Characterization of neuroendocrine cells in benign prostatic epithelium and prostatic adenocarcinoma. AUA 87th Annual Meeting, Washington, D.C., May, 1992.
112. Dalbagni G, Presti JC, Reuter VE, Fair WR, Cordon-Cardo C: The role of chromosome 17 in bladder cancer. AUA 87th Annual Meeting, Washington, D.C., May, 1992.
113. Sheinfeld J, Sarkis AS, Reuter VE, Fair WR, Cordon-Cardo C: The Lewis X antigen as a marker of neoplastic transformation in urothelium. AUA 87th Annual Meeting, Washington, D.C., May, 1992.
114. Axelrod HR, Gilman SC, D'Aleo CJ, Petrylak D, Reuter V, Gulfo JV, Saad A, Cordon-Cardo C, Scher HI: Preclinical results and human immunohistochemical studies with 90Y-CYT-356: a new prostate cancer therapeutic agent. AUA 87th Annual Meeting, Washington, D.C., May, 1992.

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117. Cote RJ, Drobnjak M, Kuhajda F, Pastemak G, Cordon-Cardo C, Rosen PP: Prognostic features in breast carcinoma: detection of occult axillary lymph node micrometastases, expression of haptoglobin related binding protein (OA519) and progesterone receptor in primary tumors. United States and Canadian Academy of Pathology 81st Annual Meeting, Atlanta, March, 1992.
118. Reuter VE, Motzer B, Lee A, Bosl G, Bander N, Cordon-Cardo C: Kidney differentiation antigen expression in human renal cell carcinoma: assessment of reactivity and clinicopathologic correlation. United States and Canadian Academy of Pathology 81st Annual Meeting, Atlanta, March, 1992.
119. Petrylak DP, Scher HI, Reuter V, O'Moore PV, Sheinfeld J, O'Brien J, Cordon-Cardo C: P-glycoprotein (PGP) expression in invasive and metastatic urothelial tract cancer (UTC). American Society of Clinical Oncology, San Diego, CA, May, 1992.
120. Armas OA, Melamed J, Aprikian A, Cordon-Cardo C, Fair W, Reuter VE: Effect of preoperative androgen deprivation therapy on prostatic carcinoma. United States and Canadian Academy of Pathology Annual Meeting, New Orleans, March, 1993.
121. Melamed J, Sarkis A, Zhang Z-F, Herr H, Cordon-Cardo C, Reuter VE: Prognostic significance of p53 protein overexpression in T1 bladder carcinoma (TCC). United States and Canadian Academy of Pathology Annual Meeting, New Orleans, March, 1993.
122. Melamed J, Sarkis A, Zhang Z-F, Herr H, Cordon-Cardo C, Reuter VE: p53 nuclear overexpression as a predictor of progression in non-invasive papillary transitional cell carcinoma (TCC) and carcinoma in situ of the bladder. United States and Canadian Academy of Pathology Annual Meeting, New Orleans, March, 1993.
123. Melamed J, Sarkis A, Zhang Z-F, Cordon-Cardo C, Reuter VE: Evaluation of clinical and histopathological prognostic parameters in T1 transitional cell carcinoma (TCC) of the urinary bladder. United States and Canadian Academy of Pathology Annual Meeting, New Orleans, March, 1993.

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125. Reuter V, Fair WR, Cordon-Cardo C: Genetic alterations in bladder cancer. Proceedings 84th Annual Meeting of the American Association for Cancer Research, Orlando, Florida, May, 1993.
126. Simak R, Cohen D, Fair WR, Scher H, Birkett NC, Melamed J, Reuter V, Cordon-Cardo C: Expression of c-kit and kit-ligand in human prostate cancer tissues. Proceedings 84th Annual Meeting of the American Association for Cancer Research, Orlando, Florida, May, 1993.
127. Latres E, Drobnjak M, Ramos M, Karpeh M, Woodruff J, Cordon-Cardo. p53 and chromosome 17 abnormalities in adult soft tissue sarcomas. Proceedings 84th Annual Meeting of the American Association for Cancer Research, Orlando, Florida, May, 1993.
128. Dalbagni G, Saez GT, Oliva MR, Reute VE, Rosai J, Fair WR, Pellicer A, Cordon-Cardo C: p53 mutations in human bladder cancer: Genotypic versus phenotypic patterns. Proceedings 84th Annual Meeting of the American Association for Cancer Research, Orlando, Florida, May, 1993.
129. Drobnjak M, Latres E, Dudas ME, Pollack D, Karpeh M, Levine A, Brennan M, Cordon-Cardo C: p53 and MDM-2 overexpression in human soft tissue sarcomas (STS): Correlations with clinicopathological parameters and tumor proliferation. Proceedings 84th Annual Meeting of the American Association for Cancer Research, Orlando, Florida, May, 1993.
130. Weiss RE, Cordon-Cardo C, Fair WR: Characterization of cathepsin B mediated protease cascade in prostate cancer cell lines. Proceedings 84th Annual Meeting of the American Association for Cancer Research, Orlando, Florida, May, 1993.
131. Aprikian AG, Sarkis AS, Fair WR, Cordon-Cardo: p53 nuclear overexpression in prostatic adenocarcinoma. AUA 88th Annual Meeting, San Antonio, Texas, May, 1993.
132. Sarkis AS, Dalbagni G, Melamed J, Cordon-Cardo C, Zhang/ Z-F, Sheinfeld J, Herr HW, Fair WR, Reuter VE: p53 nuclear overexpression in carcinoma in situ and in non-invasive papillary transitional cell carcinoma (TCC) of the bladder. AUA 88th Annual Meeting, San Antonio, Texas, May, 1993.
133. Dalbagni G, Saez GT, Oliva MR, Pellicer A, Reuter VE, Fair WR, Cordon-Cardo C: p53 mutations in bladder cancer: Correlation between immunohistochemistry (IHC), single strand conformation polymorphism (SSCP) and sequencing. AUA 88th Annual Meeting, San Antonio, Texas, May, 1993.

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141. Presti JC, San Francisco CA, Cordon-Cardo C, Lee AC, Fair WR, Reuter VE: Altered p53 expression and allelic loss on chromosome 17 in renal cell carcinoma. AUA 88th Annual Meeting, San Antonio, Texas, May, 1993.
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145. Lianes P, Orlow I, Zhang Z-F, Oliva MR, Sarkis AS, Reuter VE, Cordon-Cardo C: Altered patterns of expression of MDM2 and TP53 in bladder carcinoma. American Society of Clinical Oncology, Dallas, Texas, May, 1994.
146. Bajorin D, Sarkis A, Reuter V, Netto G, Cordon-Cardo C, Zhang Z-F, Herr H, Scher H: Invasive bladder cancer treated with neoadjuvant MVAC: The relationship of p53 nuclear overexpression with survival. American Society of Clinical Oncology, Dallas, Texas, May, 1994.
147. Zhang ZF, Zeng ZS, Sarkis AS, Limstra DS, Charytonowicz E, Guillern JG, Cordon-Cardo C, Cohen AM, Begg C: A molecular epidemiological inquiry on p53 nuclear over-expression in colorectal cancer. Proceedings 85th Annual Meeting of the American Association for Cancer Research, San Francisco, CA, April, 1994.
148. Ghossein R, Li M, Cordon-Cardo C. Sensitivity of PCR-SSCP in detecting p53 point mutations. 84th Annual Meeting of the United States and Canadian Academy of Pathology. March, 1995.
149. Chin L, Schreiber-Agus N, Cordon-Cardo C, Nisen P, DePinho RA. Expression of the myc antagonist made in normal squamous cell differentiation and its potential utility as a potent anti-tumor agent in squamous cell carcinoma. 44th Annual Symposium on the Biology of Skin. July, 1995.
150. Lee H-W., Serrano M, Chin L, Cordon-Cardo C, Beach D, DePinho RA. p16INK4a in the development of normal and neoplastic cells. Keystone Symposia. February, 1996.
151. Osman I, Pellicer I, Scher H, Zhang Z-F, Hamza R, Issa S, Khaled H. Alterations of cell cycle regulators in Bilharzial-related bladder cancers. Proceedings of the American Association for Cancer Research. March, 1996.
152. Su SL, Lacombe L, Fair WR, Dalbagni G, Cordon-Cardo C, Heston WDW. Microsatellite alterations of the prostate specific membrane antigen gene in prostate cell lines and human prostate cancer. Proceedings of the American Association for Cancer Research. March, 1996.
153. Zhang ZF, Shu XM, Cordon-Cardo C, Orlow I, Lianes P, Lacombe L, Cao P, Sarkis A, Dalbagni G, Reuter V, Scher H, Begg C. Cigarette smoking and chromosome 9 alterations in bladder cancer. Proceedings of the American Association for Cancer Research. March, 1996.

154. Osman I, Scher H, Orlow I, Lacombe L, Zhang Z-F, Cordon-Cardo C. Chromosome 16q harbors two putative tumor suppressor genes in prostate cancer. Proceedings of the American Association for Cancer Research. March, 1996.
155. Monell CR, Wu C, Shi L, Wei J, Dias P, Cordon-Cardo C, Singh S. Development of monoclonal antibodies specific for the p15 and p16 cyclin/cdk inhibitors. Proceedings of the American Association for Cancer Research. March, 1996.
156. Liegeois N, Schreiber-Agus N, Chin L, Zheng J, Silverman A, Lee H-W, Cordon-Cardo C, Serrano M, Beach D, DePinho R. Both p16/INK4a and p19/ALF act as potent negative regulators of cellular transformation. Cancer Genetics and Tumor Suppressor Genes. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. August, 1996.
157. Schreiber-Agus N, Alland L, Hou H, Muhle R, Guida P, Lee H-W, Cordon-Cardo C, DePinho R. Role of the myc antagonist, Mxi, in cellular growth control and development. Cancer Genetics and Tumor Suppressor Genes. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. August, 1996.
158. Richon VM, Venta-Perez G, Cordon-Cardo C, Rifkind RA, Marks PA, Russo P. Loss of retinoblastoma protein function leads to induction of apoptosis in bladder carcinoma cells by hybrid polar agents rather than induction of differentiation. Cancer Genetics and Tumor Suppressor Genes. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. August, 1996.
159. Latres E, Cordon-Cardo C, Barbacid M. Targeted disruption of the p15 gene: A negative cell cycle regulator. ASEICA, Madrid, 1996.

WORKSHOPS, COURSES AND LECTURES

1. La Recerca a l'Universitat. 3er Congres Universitari Catala. Barcelona, Spain. 1978.
2. La Cel.lula Cebada: Biologia Cel.lular i Molecular. Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, August 1982.
3. Els Anticosos Monoclonals en la Anatomia Patologica. Col.legi de Metges de Catalunya i Balears, Barcelona, Spain, December 1982.
4. Tumor associated antigens detected by monoclonal antibodies. USA-Japan Automated Cytology Conference, New York, February 1983.
5. Tumor Immunopathology: Principles and Practices. State University of New York, New York, February 1983.
6. Immunohistochemistry: Methodology and Clinicopathological Applications. University of Puerto Rico, San Juan, Puerto Rico, April 1983.
7. Principles of Immunopathology. Universidad del Caribe - School of Medicine, Cayey, Puerto Rico, April 1983.
8. Immunopathology of the Urinary Tract Neoplasms. Advanced Course of Surgical Pathology - Memorial Sloan-Kettering Cancer Center, New York, May 1983.
9. Tumor Associated Antigens and Immunopathology of Tumors. Combined Meeting Memorial Hospital Sloan-Kettering Institute, New York, June 1983.
10. Monoclonal Antibodies Detecting Associated Antigens of Human Solid Tumors. Memorial Sloan-Kettering Cancer Center, Medical Grand Rounds, July 1983.
11. Inmunohistoquimica Diagnostics. Hospital de la Concepcion-Fundacion Jimenez-Diaz, Universidad Autonoma de Madrid, Spain, December 1983.
12. Anticuerpos Monoclonales en Diagnostico Clinico y Patologico. Hospital de San Carlos, Universidad Central de Madrid, Spain, December 1983.
13. Workshop in Immunopathology. Academia de Ciencias Medicas de Catalunya i Balears, Barcelona, Spain, December 1983.
14. Sindrome de Inmunodeficiencia Adquirida: Consideraciones Patologicas e Inmunopatologicas. Hospital Clinico de Barcelona, Universidad Central, Barcelona, Spain, December 1983.

15. Use of Monoclonal Antibodies in the Study of Human Cancer. New York University Hospital, Immunology Seminar Series, New York, January 1984.
16. Monoclonal Antibodies Defining Differentiation Antigens. Memorial Sloan-Kettering Cancer Center, Pediatric Grand Rounds, New York, January 1984.
17. Antigens of Melanocytes and Melanoma Cells. New York University Hospital, Dermatopathology Seminar, New York, February 1984.
18. Tumor Immunopathology. New York University Hospital, Pathology Grand Rounds, New York, April 1984.
19. Inmunopatología del Sistema Genital Femenino. Simposium Internacional de Patología Ginecológica, Alicante, Spain, April 1984.
20. Panel on Immunodiagnosis. International Union Against Cancer, Bonn, Federal Republic of Germany, May 1984.
21. Tumor Immunopathology: Use of Monoclonal Antibodies. Advanced Course of Surgical Pathology, Memorial Sloan-Kettering Cancer Center, New York, May 1984.
22. Role of Immunohistochemical Stains in the Diagnosis of Connective Tissue Tumors. Advanced Course of Soft Tissue Tumors, Memorial Sloan-Kettering Cancer Center, New York, September 1984.
23. Monoclonal Antibodies in Diagnosis of Renal and Urothelial Tumors. Immunocytochemistry Workshop in Tumor Diagnosis, Detroit, October 1984.
24. Analysis of a Phase I Trial Monoclonal Antibody Immunotherapy in Melanoma. Surgical Pathology Grand Rounds, Memorial Hospital, New York, December 1984.
25. Diagnostico Inmunohistoquímico de las Neoplasias Mediante Anticuerpos Monoclonales. International Symposium on Monoclonal Antibodies and their Clinical Utility. Barcelona, Spain, January 1985.
26. Anticòsos Monoclonal: Immunodiagnostic i Immunoterapia. Reial Acadèmia de Medicina de Catalunya i Balears, Barcelona, Spain, January 1985.
27. The Use of Immunoperoxidase in the Diagnosis of Surgical Pathology - Workshop. University of Puerto Rico, San Juan, Puerto Rico, February 1985.

28. Panel on Immunodiagnosis. International Union Against Cancer, Bonn, Federal Republic of Germany, April 1985.
29. The Use of Monoclonal Antibodies as a Diagnostic Tool. Advanced Course of Surgical Pathology of Neoplastic Diseases, Memorial Sloan-Kettering Cancer Center, New York, May 1985.
30. Detection of Oncogene Products in Human Tumors. New York State Society of Pathologists, Annual Meeting, New York, September 1985.
31. Monoclonal Antibodies in Tumor Diagnosis. Tutorial and Workshop in the Use of Immunocytochemistry and Electron Microscopy in Tumor Diagnosis, Detroit, October 1985.
32. Immunocytochemistry of Tumors of Kidney and Urothelium. Tutorial and Workshop in the Use of Immunocytochemistry and Electron Microscopy in Tumor Diagnosis, Detroit, October 1985.
33. Oncogenes and Coded Proteins in Human Tumors. Special Program in Immunopathology, ASCP/CAP Meeting, Las Vegas, November 1985.
34. Dissection of the Human Urinary Tract by Monoclonal Antibodies: Analysis of Kidney and Bladder Tumors. Research Seminar, Montefiore Hospital and Medical Center, Albert Einstein College of Medicine, New York, December 1985.
35. Monoclonal Antibodies in Urinary Tract Tumors. Scientific Conference, Harlem Hospital, College of Physicians and Surgeons of Columbia University, New York, January 1986.
36. Workshop in the Use of Immunocytochemistry in Pathology. University Hospital "R. Ruiz Arnau" - Universidad Central del Caribe School of Medicine, Puerto Rico, March 1986.
37. Immunopathologic Analysis of Solid Tumors. University of Southern California, Los Angeles, April 1986.
38. The Use of Monoclonal Antibodies in Surgical Pathology. Surgical Pathology of Neoplastic Disease/Advanced, Memorial Sloan-Kettering Cancer Center, New York, May 1986.
39. Panel on Immunodiagnosis. International Union Against Cancer, Bonn, Federal Republic of Germany, June 1986.
40. Immunoanatomic Dissection of the Human Urinary Tract. Medical Oncology Research Conference, Memorial Sloan-Kettering Cancer Center, July 1986.
41. Workshop: Immunohistochemistry and Immunopathology. Beijing Cancer Research Center, Beijing, People's Republic of China, September 1986.

42. Immunology and Immunopathology: The Use of Immunohistochemistry in Microanatomy and Pathology. University of Shanghai Medical School, Shanghai, People's Republic of China, September 1986.
43. Immunopathology of Human Solid Tumors. Medical Oncology - Solid Tumor Conference. Memorial Sloan-Kettering Cancer Center, New York, October 1986.
44. Immunopathology: How is it Done. Alumni Meeting Scientific Conference, Memorial Sloan-Kettering Cancer Center, New York, November 1986.
45. Immunology and Immunopathology of Renal Cell Carcinomas. Memorial Sloan-Kettering Cancer Center, New York, November 1986.
46. Inmunopatologia en Tumores Solidos: Inmunohistoquímica en Patología Quirúrgica. Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, December 1986.
47. Differentiation Antigens, Proto-Oncogenes and Oncogenes in Human Normal and Neoplastic Tissues. Nassau County Pathology Club, New York, January 1987.
48. Oncogenes, Growth Factors and Differentiation Antigens in Human Normal and Abnormal Tissues. Universidad Central del Caribe School of Medicine, Puerto Rico, February 1987.
49. Monoclonal Antibodies in Surgical Pathology. Surgical Pathology of Neoplastic Disease/Advanced, Memorial Sloan-Kettering Cancer Center, New York, May 1987.
50. Immunology and Immunopathology of Intermediate Filament Antigens. University Hospital "R. Ruiz Arnau" - Universidad Central del Caribe School of Medicine, San Juan, Puerto Rico, May 1987.
51. Inmunopatologia de Filamentos Intermedios y Antigenos de Diferenciación. Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, June 1987.
52. p21^{ras} Proto-Oncogene and Oncogene product(s) in Human Normal and Tumor Tissues. New York University School of Medical Sciences, New York, July 1987.
53. Antigens and Antigenic Systems of the Human Nephron. Research Seminar, Urology Service, Memorial Sloan-Kettering Cancer Center, New York, July 1987.
54. Immunology and Immunopathology of URO Antigens. Oncogene Science Laboratories, New York, August 1987.

55. Blood Group Related Antigens in Human Normal Tissues and Tumors. Cytogen Laboratories, Princeton, New Jersey, September 1987.
56. Human Genetics and Molecular Genetics. Universidad Central del Caribe School of Medicine, San Juan, Puerto Rico, November 1987.
57. Anticòsos Monoclonals: Utilitat Diagnostics i de Pronostic a la Patologia Tumoral. Hospital General Vall d'Hebron, Universidad Autonoma, Barcelona, Spain, December 1987.
58. Differentiation Antigens of Renal Tumors and Transitional Cell Carcinomas. Department of Pathology Grand Rounds, Memorial Sloan-Kettering Cancer Center, New York, January 1988.
59. Immunopathology Analyses of Clinical Trials in Melanoma Patients. Department of Medicine Grand Rounds, Mayo Clinic, Rochester, March 1988.
60. Differentiation Antigens of Melanocytes and Melanoma. Dermatology Service, Special Seminar, Mayo Clinic, Rochester, March 1988.
61. Immunoanatomic Dissection of the Human Nephron and Immunopathology of Genitourinary Tumors. Medical Research Conference, Hospital for Special Surgery, New York, March 1988.
62. Monoclonal Antibodies as Tumor Markers in Surgical Pathology. Surgical Pathology of Neoplastic Disease/Advanced, Memorial Hospital, New York, May 1988.
63. Seminar and Workshop on Immunohistochemistry. The Use of Tumor Markers in Surgical Pathology. Shanghai University Second Medical School, Shanghai, People's Republic of China, June 1988.
64. Seminar on Molecular Immunopathology of Cancer. Beijing Cancer Research Center, Beijing, People's Republic of China, June 1988.
65. Molecular Immunopathology: Tumor Markers for Diagnosis, Prognosis and Selection of Therapy. Rochester Oncology Society, Mayo Clinic Foundation, Rochester, September 1988.
66. Identifying the Phenotype of Multidrug Resistant Tumor Cells. Special Seminar, Medical Oncology, Mayo Clinic, Rochester, September 1988.
67. Immunohistochemistry in Oncologic Surgical Pathology. Pathology Grand Rounds, Memorial Hospital, New York, October 1988.

68. Expression of P-glycoprotein in the Blood-Brain Barrier. Board of Scientific Consultants, Memorial Hospital, New York, November 1988.
69. Avencos en Immunohistoquímica i Hibridització Mol. Iecular. Associació d'Anatomia Patològica, Acadèmia de Medicina de Catalunya i Balears, Barcelona, Spain, December 1988.
70. Resistència Tumoral a Múltiples Fàrmacs. Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain, December 1988.
71. MDR1 Gene Expression in Human Normal and Tumor Cells. Research Seminar Radiation Oncology Service, Memorial Hospital, New York, January 1989.
72. Blood Group Antigen in Normal Urothelium and Bladder Tumors. Journal Club, Rush-Presbyterian Medical Center, Chicago, January 1989.
73. Multidrug Resistance: Expression of P-glycoprotein in Normal and Tumor Tissues. Special Lecture, Rush-Presbyterian Medical Center, Chicago, January 1989.
74. Immunobiology of Melanocytes: Nevi and Melanoma. American Society of Dermatopathology-International Academy of Pathology, San Francisco, March 1989.
75. P-glycoprotein Expression in Human Tumors. American Association of Pathologists - FASEB Meeting, New Orleans, March 1989.
76. Detection of the Multidrug Resistance Gene Product in Human Tumors and Normal Tissues. Department of Pathology, MSKCC, New York, March 1989.
77. Blood Group Antigens as Tumor Markers in Pathology. Cancer Research Institute, New York, April 1989.
78. Differentiation Antigens of Human Sarcoma. Solid Tumor Service Conference. Memorial Sloan-Kettering Cancer Center, New York, April 1989.
79. Tumor Markers in Gastrointestinal Oncologic Pathology. National Cancer Institute, Colon Cancer Study Group, Bethesda, Maryland, May 1989.
80. Differentiation Antigens of Bladder Tumors: Markers for Prognosis and Selection of Therapy. XII European Congress of Pathology, Porto, Portugal, September 1989.
81. Expression of the Multidrug Resistance Gene Product in Human Normal and Tumor Tissues. XIV Annual Memorial Hospital Alumni Society, September 1989.

82. Tumor Markers in Diagnostic Pathology. Medical Association of Puerto Rico, San Juan, Puerto Rico, November 1989.
83. Immunopathology Markers for Bladder Tumors. Bladder Marker Network, New York, November 1989.
84. Molecular Immunopathology in Oncology. Academia de Ciencies Mediques de Catalunya i Balears, Barcelona, Spain, December 1989.
85. Tumor Markers in the Diagnosis and Prognosis of Human Cancer. Instituto di Tumori Regina Elena, Rome, Italy, January 1990.
86. Altered Expression of Oncogenes and Tumor Suppressor Genes in Human Tumors. National Hellenic Research Foundation, Athens, Greece, January 1990.
87. Multidrug Resistance in Human Tumors. International Academy of Pathology. Boston, March 1990.
88. Expression of P-glycoprotein in Human Normal and Tumor Tissues. Montefiore Hospital, Albert Einstein College of Medicine, New York, April 1990.
89. Molecular Immunopathology in the Diagnosis of Human Cancer. Squibb Institute for Medical Research, Princeton, April 1990.
90. Seminar in Immunopathology. Advanced Course on Surgical Pathology of Neoplastic Diseases. Memorial Sloan-Kettering Cancer Center, New York, May 1990.
91. Workshop on Molecular Immunopathology. Spanish Academy of Pathology, Barcelona, Spain, June 1990.
92. Biological Markers in Human Tumors. XVIII International Congress of the International Academy of Pathology, Buenos Aires, Argentina, September 1990.
93. Multidrug Resistance Genes and Their Products in Human Normal Tissues and Tumors. Squibb Institute for Medical Research, Princeton, September 1990.
94. The Use of Monoclonal Antibodies in Cancer Diagnosis and Therapy. American College of Surgeons, San Francisco, October 1990.
95. Immunopathology and Molecular Markers of Bladder Cancer. Prouts Neck, Maine, October 1990.

96. The Retinoblastoma Gene and Encoded Product in Human Tumors. New York University Medical Center, New York, October 1990.
97. Monoclonal Antibodies in Diagnosis and Therapy. American College of Surgeons, San Francisco, October 1990.
98. Molecular Immunopathology Analysis of Human Bladder Tumors. Columbia Presbyterian Hospital, New York, March 1991.
99. Molecular Immunopathology in the Diagnosis and Prognosis of Cancer. Spanish Academy of Oncology, Mallorca, Spain, May 1991.
100. Oncogenic Mechanisms in Human Solid Tumors: Oncogenes and Tumor Suppressor Genes. Hospital Oncologic "Duran i Reynals", Barcelona, Spain, May 1991.
101. Tumor Markers in Human Cancer. National Corporation of Medical Associates, Memorial Hospital, New York, June 1991.
102. Role of Tyrosine Kinases in Prostate Cancer. Squibb Bristol Myers Research Institute, Princeton, New Jersey, August 1991.
103. Expression of the Multidrug Resistant Gene Produce in Human Normal and Tumor Tissues. The Second Robert Steel Foundation International Symposium, MSKCC, New York, September 1991.
104. Tumor Suppressor Gene Loss in Human Bladder Cancer. AACR/EACR Symposium, Santa Margherita Ligure, Italy, November 1991.
105. Markers of Response to Therapy in Pathology. Applied Immunopathology Society, New York, November 1991.
106. Molecular Immunopathology of Urothelial Tumors: Diagnostic and Prognostic Markers. International Academy of Pathology, Atlanta, March 1992.
107. Molecular Markers for Tumor Progression. Radiation Research Society, Salt Lake City, Utah, March 1992.
108. Molecular Immunopathology of Bladder Cancer Progression. Fox Chase Cancer Center, Philadelphia, April 1992.
109. Role of Immunocytochemistry and Molecular Probing in Diagnostic Cytology. The Greater New York Association of Cytotechnologists Annual Meeting, New York, April 1992.

110. Mechanisms of Multistage Carcinogenesis in Human Solid Tumors. Symposium on Cancer as a Genetic Disease, Rome, Italy, May 1992.
111. P-glycoprotein Expression During Fetal Kidney Development: A Model of Pgp Expression in Renal Cell Carcinomas. American Association of Cancer Research, San Diego, May 1992.
112. Multistage Carcinogenesis in bladder Cancer. Jefferson Cancer Center, Philadelphia, August 1992.
113. Genetic Disturbances in the Development and Progression of Human Bladder Cancer. American Urological Association, Houston, August 1992.
114. Workshop on Predictive Markers in Clinical Cancer: Assessment and Application. National Cancer Institute, Bethesda, September 1992.
115. Biology of Progression of Bladder Cancer. International Academy of Pathology, Madrid, Spain, October 1992.
116. Drug Resistance in Human Tumors: Molecular Mechanisms and Clinical Implications. International Academy of Pathology, Madrid, Spain, October 1992.
117. Differential Expression of Multidrug Resistant Genes in Human Tumors. Universidad Internacional "Menendez y Pelayo", Cuenca, Spain, November 1992.
118. Oncogenes y Anticuerpos Monoclonales en Uro-Oncologia. V Jornadas de Actualizacion Urologica, Madrid, Spain, November 1992.
119. The Biology of Bladder Cancer Progression. Special Course - Molecular Pathology - '93, New Insights into Cancer Provided by Advances in Molecular and Cellular Biology, United States and Canadian Academy of Pathology, New Orleans, March 1993.
120. Approaches to Cancer Prevention and Early Diagnosis. Precursor Lesions of Bladder Carcinoma, Montreux, Switzerland, March 1993.
121. Molecular Biology of Tumor Progression in Bladder Cancer. The Cleveland Clinic Foundation, Grand Rounds, Cleveland, April 1993.
122. Implications of Chromosome 9 Deletions in Bladder Cancer. Second International Chromosome 9 Workshop, Chatham, Massachusetts, April 1993.
123. Differential Expression of P-Glycoprotein in Human Normal and Tumor Tissues. Arizona Cancer Center, Tucson, Arizona, May 1993.

124. Oncogenes y Genes de Supresion Tumoral en Neoplasias Humanas. XVI Congreso Nacional de la Sociedad Espanola de Anatomia Patologia, Tenerife, Spain, May 1993.
125. Molecular Genetics of Bladder Cancer. NCI Bladder Tumor Marker Network, Symposium of Bladder Cancer, Quebec, Canada, June 1993.
126. Molecular Markers for the Early Detection and Prognosis of Bladder Carcinoma. National Corporate Medical Associates Program, Memorial Sloan-Kettering Cancer Center, New York, June 1993.
127. Tumor Suppressor Genes: Biological and Clinical Implications, European Society for Clinical Investigation Annual Scientific Meeting, Las Palmas de Gran Canaria, Spain, September 1993.
128. New Perspectives in Tumor Markers in Patient Care. ASCP/CAP Meeting, Orlando, Florida, October 1993.
129. p53 and Retinoblastoma Gene in Bladder Cancer. Prouts Neck Bladder Cancer Conference, Prouts Neck, Maine, October 1993.
130. Molecular Alterations Associated with Bladder Cancer Progression. University of Cincinnati Medical Center, Cincinnati, October 1993.
131. Biology of Progression of Bladder Cancer. Workshop on Immunohistochemistry and Molecular Diagnosis in Tumor Pathology, Fox Chase Cancer Center, Philadelphia, November 1993.
132. Oncogens i Gens Supresors en la Progressio del Cancer Huma. Institut de Recerca Oncologica de Barcelona, Barcelona, Spain, November 1993.
133. Oncogenes and Anti-Oncogenes: From the Laboratory to the Bedside. Symposium Internacional de Biomedicina, Universitat de Lleida, Spain, November 1993.
134. New Findings of the Molecular Characterization of Urothelial Tumors. Altered Expression of Rb and p53 Mutations in Bladder Cancer Progression. The Second Annual Genitourinary Oncology Conference, "Malignant Diseases of the Urothelium," MD Anderson Cancer Center, Houston, Texas, January 14-15, 1994.
135. Altered Patterns of Tumor Suppressor Genes in Human Tumors: Clinical Implications. Keystone Symposium, Tumour Suppressor Genes, Taos, New Mexico, February 13-20, 1994.

136. The Molecular Basis of Cancer: Clinical Applications, Bristol Meyers Squibb Pharmaceutical Research Institute, Segovia, Spain, April 14-16, 1994.
137. Tumor Suppressor Genes as Prognostic Markers in Human Cancer. Workshop on Cell Proliferation and Differentiation of the Annual Scientific Meeting of the European Society for Clinical Investigation (ESCI), Toledo, Spain, April 21-23, 1994.
138. P-glycoprotein Detection Utilizing Immunohistochemical Assays. MDR Detection Methods Workshop. St. Jude Children's Hospital, Memphis, April 29-30, 1994.
139. Techniques in Tumor Pathology: An Overview. Surgical Pathology of Neoplastic Disease, Memorial Sloan-Kettering Cancer Center, New York, May 2-6, 1994.
140. Mutations of Cell Cycle Kinase Inhibitors in Human Cancer. Bristol Myers Squibb Research Institute, Princeton, May 9, 1994.
141. Molecular Pathology of Genetic Markers for Cancer. Workshop on Cancer Genetics. Imperial Cancer Research Foundation, London, England, June 25-27, 1994.
142. Tumor Suppressor Genes in Human Cancer. Fourth International Symposium on Oncogenes and Tumor Suppressor Genes, San Sebastian, Spain, September 7-9, 1994.
143. Tumor Suppressor Genes and Bladder Cancer Progression. Symposium on Oncogenes, Tumor Antigens and MHC Molecules, Jaen, Spain, October 6-8, 1994.
144. Molecular Abnormalities Associated with Bladder Cancer Progression. USC/Norris Comprehensive Cancer Center, Los Angeles, October 19-20, 1994.
145. Alterations of Cell Cycle Regulators in Bladder Cancer. Society for Basic Urologic Research Fall Symposium, Stanford, October 20-23, 1994.
146. Advances in Tumor Markers: Background and Application to Bladder Cancer. ASCP/CAP Meeting, Washington, D.C., October 23-26, 1994.
147. Tumor Suppressor Genes in Soft Tissue Sarcomas. Current Concepts in the Pathology of Soft Tissue Neoplasms, Memorial Hospital, November 1-2, 1994.
148. Perspectives on the Analysis of Genetic Factors in the Etiology of Human Tumors. Scientific Session to Homage to "Prof. Dr. Antoni Subias." Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain, December 15, 1994.
149. Molecular Pathology in the Diagnosis and Prognosis of Human Cancer. Workshop on New Advances in Clinical Medicine. Clinica Moncloa, Madrid, December 15-16, 1994.

150. The Molecular Pathology of Tumor Progression. Special Seminar. MetPath Laboratories, New Jersey, January 5, 1995.
151. Tumor Suppressor Genes in Human Cancer. Keynote Lecturer. Fifth International Symposium on Biology and Clinical Usefulness of Tumor Markers, Barcelona, Spain, February 8-11, 1995.
152. Organization of Clinical and Molecular Pathology Laboratories. Eighth Biannual Meeting of the Swedish Pathology Association, Uppsala, Sweden, March 2-4, 1995.
153. Tumor Progression in Bladder Cancer: Ordered Sequence or Chaotic Consequence? Eighth Biannual Meeting of the Swedish Pathology Association, Uppsala, Sweden, March 2-4, 1995.
154. Molecular Pathology of Bladder Cancer. Karolinska Hospital, Stockholm, Sweden, March 6, 1995.
155. Tumor Suppressor Genes. American Cancer Society National Conference on Gynecological Cancers, Washington, D.C., April 6-8, 1995.
156. Molecular Alterations Associated with Bladder Carcinoma Progression. Surgical Pathology of Neoplastic Diseases, Florence, Italy, May 1-5, 1995.
157. Tumor Suppressor Genes in Soft Tissue Tumors. Surgical Pathology of Neoplastic Diseases, Florence, Italy, May 1-5, 1995.
158. Molecular Characterization of Colorectal Carcinoma Progression. Surgical Pathology of Neoplastic Diseases, Florence, Italy, May 1-5, 1995.
159. Molecular Basis of Cancer. Academia de Ciencias Medicas, Barcelona, Spain. June 26, 1995.
160. Advances in Tumor Markers: Background and Application to Bladder Cancer. The American College of Pathologists, Fall National Meeting, New Orleans, September 21, 1995.
161. Mutations of Negative Regulators of Cell Cycle: Clinical Implications in Human Cancer. VI Congreso of the Asociacion Espanola de Investigacion sobre el Cancer (ASEICA), Barcelona, Spain, September 26, 1995.
162. Molecular Alterations Affecting the p53 Control Pathway in Human Cancer. Grand Rounds, New York Medical College, Valhalla, New York, October 18, 1995.
163. The Retinoblastoma Tumor Suppressor Gene in Human Cancer. 45th Annual Meeting, American Society of Human Genetics, Indianapolis, MN, October 25, 1995.

164. Bladder Cancer: A Clinical Model for Human Carcinogenesis. 43rd Annual Meeting of the American Society of Cytopathology, New York, November 9, 1995.
165. Mutations Affecting Genes Involved in Cell Cycle Control in Human Solid Tumors. Surgical Research Conference, Memorial Sloan-Kettering Cancer Center, New York, November 13, 1995.
166. Mechanism of Radiation-Induced Damage to the Mouse Wing. The Twentieth Annual Alumni Program, Memorial Sloan-Kettering Cancer Center, New York, November 17, 1995.
167. Mutation of Cell Cycle Regulators in Human Cancer and Effects of INK4A Deficiency on Tumor Susceptibility. Albany Medical College, Albany, New York, December 1, 1995.
168. Biological and Clinical Implications of Mutations Affecting Oncogenes and Tumor Suppressor Genes in Human Cancer. Academia Medico-Quirurgica Espanola, Madrid, Spain, December 11, 1995.
169. Molecular Alterations Affecting p16/INK4A in Human Cancer. Grand Rounds, New York Medical College, Valhalla, New York, January 16, 1996.
170. Biological and Clinical Implications of p16/INK4a Mutations. Special Seminar, Kenneth Norris Cancer Center, University of South California, Los Angeles, January 26, 1996.
171. Genetic Basis of Cancer and Gene Therapy. Arab Society of Chemotherapy. Cairo, Egypt, March 14, 1996.
172. Molecular Models of Tumor Progression in Bladder Cancer. National Cancer Institute of Egypt, Cairo, Egypt, March 16, 1996.
173. Molecular Alterations of p16/INK4A: Biological and Clinical Implications. The Kimmel Cancer Institute Seminars, Kimmel Cancer Center/Jefferson Medical College, Philadelphia, April 4, 1996.
174. Functional and Immunophenotypic Analysis of Tumor Suppressor Genes. Conjoint Conference - Soft Tissue Sarcoma, Memorial Sloan-Kettering Cancer Center, New York, April 15, 1996.
175. Molecular Alterations Associated With Bladder Cancer Progression. XIII Reunion Nacional Del Grupo Uro-Oncologico, Barcelona, Spain, April 19-20, 1996.
176. Mutations in Cell Cycle Control Genes Related to Initiation and Progression of Solid Tumors. I Jornada Sobre Biologia Molecular i Genetica de Tumors Solids. Sant Pau Institut de Recerca, Universitat de Barcelona, Barcelona, Spain, April 18, 1996.
177. Is p53/RB Important for Therapeutic Outcome? Controversial Sessions of the 87th Annual Meeting of the Association for Cancer Research, Washington, D.C., April 24, 1996.

178. Mutations of Cell Cycle Regulators in Bladder Cancer. Society for Basic Urological Research 1996 Spring Meeting, Orlando, Florida, May 4, 1996.
179. Molecular Alterations Associated With Tumor Progression and The Practical Utility of Tumor Suppressor Genes. Advanced Surgical Pathology of Neoplastic Diseases, Memorial Sloan-Kettering Cancer Center, New York, May 6, 1996.
180. Molecular Mechanisms of Neoplasia. American Society for Investigative Pathology, New Orleans, June 2, 1996.
181. Biological and Clinical Implications of Mutations in Cell Cycle Genes. 16th Annual Cancer Conference, University of South Florida College of Medicine, Longboat Key, Florida, June 21-23, 1996.
182. Aplicaciones de la Biologia Molecular a la Clinica Oncologica. V Simposium sobre Oncogenes, San Sebastian, Spain, October 2-5, 1996.
183. Classic and Molecular Pathology: Integration or Separation? "C.G. Ahlstrom Lecture," Swedish Society of Pathology, National Meeting of The Swedish Medical Society, Stockholm, Sweden, November 27-29, 1996
184. Cyclin-Dependent Kinase Inhibitors: Biological and Clinical Significance. University of Uppsala, Sweden, November 29, 1996.
185. Cell Cycle Kinase Inhibitors in Human Cancer. Grand Rounds, Pathology Department, Yale University Hospital, New Haven, Connecticut, December 19, 1996.
186. Molecular Alterations Associated with Soft Tissue Sarcomas. The New York Pathological Society - New York Academy of Medicine, New York, January 16, 1997.
187. Molecular Biology of Cancer: A Colloquium on Molecular Medicine. Reial Academia de Medicina de Catalunya, Barcelona, Spain, February 11, 1997.
188. Genetic Alterations Associated with Cancer Progression in Solid Tumors. Hospital de Barcelona, Barcelona, Spain, February 13, 1997.
189. Molecular Pathology: Clinical Implications. VI International Symposium on Biology and Clinical Usefulness of Tumor Markers. Barcelona, Spain, February 14, 1997.
190. Cyclin-Dependent Kinase Inhibitors in Development and Tumorigenesis. Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey, February 24, 1997.
191. p53 as a Biological Determinant in Human Cancer. Cold Spring Harbor, New York, March 7, 1997.

192. Dysregulation of Cell Cycle Control Check Points in Human Solid Tumors. CompuCyte Laboratories, Cambridge, Massachusetts, March 20, 1997.
193. Bladder Cancer Biology and Molecular Determinants of Diagnosis and Progression. Society of Urologic Oncology, New Orleans, Louisiana, April 12, 1997.
194. Molecular Alterations in Bladder Cancer Progression. Cancer Prevention Seminar Series. Memorial Sloan-Kettering Cancer Center, New York, April 18, 1997.
195. Tumor Markers and Biological Determinants of Bladder Cancer. International Workshop on Diagnostic and Prognostic Markers in Bladder Cancer. Barcelona, Spain, May 4-7, 1997.
196. Alterations of Cell Cycle Regulators in Human Cancer. Nuclear Medicine Research Seminar Series. Memorial Sloan-Kettering Cancer Center, New York, May 19, 1997.
197. Cyclin-Dependent Kinase Inhibitors as Growth Suppressors in Human Neoplasia. Summer University Course "Understanding the Genetics of Cancer Susceptibility." Karolinska Institut, Stockholm, Sweden, June 14-17, 1997.
198. Cancer as Aberrant Cell Cycle Control. "1997 Sam Latt Conference on Molecular Pathology of Human Cancer." University of Toronto, Toronto, Canada, June 20-22, 1997.
199. Understanding the Molecular Biology Alterations of Cancer. Plenary Lecture "I Curso sobre Cancer: Del Laboratorio a la Clinica." Universidad Complutense de Madrid, San Lorenzo del Escorial, Spain, July 7-10, 1997.
200. La Genetica Predictiva - Cual es el Futuro del Diagnostico Precoz del Cancer? "El Proyecto Genoma, su Significado y Divulgacion: Mas alla de la Anatomia del DNA Humano." Universidad Internacional Menendez Pelayo, Santander, Spain, August 11-15, 1997.
201. Inhibitors of Cell Cycle in Cancer. Centre de Recherche de l'Universite Laval, Quebec, Canada, September 25, 1997.
202. The INK4 Genes and their Products in Cell Cycle Control and Cancer. Pathology Grand Rounds, Memorial Sloan-Kettering Cancer Center, New York, October 16, 1997.
203. Soft Tissue Sarcomas: Clinical and Molecular Aspects. Center Lecture Series, Memorial Sloan-Kettering Cancer Center, New York, October 20, 1997.
204. Cell Cycle Regulators as Prognostic Factors for Bladder Cancer. "VI Heinrich Warner Stiftung Symposium: Invasive Bladder Carcinoma: Progress in Basic Research and Therapy." Hamburg, Germany, October 30 to November 1, 1997.
205. Kinase Inhibitors in Cell Cycle and Human Cancer. New York Medical College, Valhalla, November 12, 1997.

206. Alterations of Cell Cycle Inhibitors in Human Cancer. University of South Florida, College of Medicine, and The H. Lee Moffitt Cancer Center, Visiting Professor, Tampa, February 9, 1998.
207. Frontiers Lecture Series: Cell Growth. XIX ISAC International Congress, Colorado Springs, March 1, 1998.
208. Inhibitors of Cell Cycle in Oncology. Academia de Ciencies Mediques de Catalunya I de Balears, Barcelona, March 26, 1998.
209. Alterations of Gens Involved in Cell Cycle and Apoptosis in Cancer. ASIP Course in Pathobiology for Basic Scientists: Neoplasia. ASIP International Congress, San Francisco, April 18, 1998.
210. Bladder Cancer. Human Genetics and Human Cancer, MSKCC, New York, May 1, 1998.
211. The Surgical pathologists and the Cell Cycle. XXI Annual Course on Surgical Pathology of Neoplastic Diseases, MSKCC, New York, May 4, 1998.
212. Alteraciones del Ciclo Celular en Procesos Neoplasicos. "Ciclo de Conferencias sobre Investigacion y Siglo XXI. Fundacion Jose Casares Gil y La Real Academia de Farmacia," Madrid, Spain, June 3, 1998.
213. Molecular Alterations of Cell Cycle Regulators in Bladder Cancer: Biological and Clinical Implications. "25th Silver Jubilee FEBS Meeting," Copenhagen, Denmark, July 9, 1998.
214. Cell Cycle and Cancer. AACR Workshop on Molecular Biology and Pathology of Neoplasia. Keystone, July 14, 1998.
215. The p53 Pathway: The Impact of p53 Status on the Clinical Treatment of Cancer. Gordon Research Conference of Chemotherapy of Experimental and Clinical Cancer. Colby-Sawyer College, New Hampshire, July 28, 1998.
216. El Mundo de la Genomica: Aplicaciones Medicas e Implicaciones Sociales. Course Director. Universidad Internacional Menendez Pelayo, Santander, Spain, August 3-7, 1998.
217. Cell Cycle Regulators in Cancer: Clinical Aspects. "VI Symposium on Oncogenes," Fundacion Ramon Areces, Madrid, Spain, October 5, 1998.
218. Introduction to Workshop: Molecular Markers of Prognosis in Bladder Cancer. Second International Workshop on Bladder Tumor Markers. Organizing Committee. Barcelona, Spain, October 15-17, 1998.
219. Molecular Pathology in Oncology: Defining Predictive Markers. Kaplan Cancer Center Series, New York University Medical Center, New York, December 16, 1998.

220. Molecular Markers in Bladder Cancer. VII International Symposium on Biology and Clinical Usefulness of Tumor Markers. Barcelona, Spain, February 5, 1999.
221. Molecular Pathology of Cancer: Developing Prognosis and Designing Treatment. The Ramon y Cajal Lectures. The Spanish Institute, New York, February 16, 1999.
222. Aplicaciones Clinicas de la Patologia Molecular en Oncologia. Hospital Clinico de la Universidad Central de Barcelona. Barcelona, Spain, April 20, 1999.
223. Conferencia Magistral: "Aplicaciones de la Patologia Molecular a Marcadores Geneticos que Determinan Protocolos de Tratamiento Clinico." VIII Congreso de la Asociacion Espanola de Investigacion sobre el Cancer. Sitges, Barcelona, Spain, April 21, 1999.
224. Predicting Clinical Outcomes in Bladder Cancer: A Molecular Approach. Advanced Course in Surgical Pathology of Neoplastic Diseases. Granada, Spain, May 3-7, 1999.
225. The Molecular Pathology of Breast Carcinoma. Defining Therapeutic Targets. Advanced Course in Surgical Pathology of Neoplastic Diseases. Granada, Spain, May 3-7, 1999.
226. Molecular Findings of Significance in the Evaluation of Soft Tissue Tumors. Advanced Course in Surgical Pathology of Neoplastic Diseases. Granada, Spain, May 3-7, 1999.
227. Cell Cycle Regulators and Their Implications in Human Cancer. Cancer Center Seminar Series Speaker. UCSF Cancer Center, San Francisco, June 9, 1999.
228. Determinantes Geneticos como Base de las Estrategias Terapeuticas. Curso Internacional de Actualizaciones en Oncologia. Universidad del Pais Vasco. San Sebastian, Spain, July 1, 1999.
229. Lecture Session on Cancer Progression: Molecular Pathology Studies. AACR Workshop: Pathobiology of Cancer, Keystone, Colorado, July 22, 1999.
230. Predictive Markers of Solid Tumors. 17th European Congress of Pathology. Co-Chair Symposium 1: "Relevant Topics in Molecular Pathology," Barcelona, Spain, September 18-23, 1999.
231. Closing of the "First Ramon y Cajal Lectures Series," Centro Medico Teknon, Barcelona, Spain, October 7, 1999.
232. Molecular Pathology of Breast and Prostate Cancer. 1st Combined Symposium in Breast and Prostate Cancer – European Society of Medical Oncology. Barcelona, Spain, October 21-22, 1999.

233. Molecular Analysis of Cell Cycle Alterations in Solid Tumors. Annual Meeting of the Association for Molecular Pathology, St. Louis, November 5-7, 1999.
234. The p27 Suppressor Gene: From Phenotype to Genotype and Back. 24th Annual Alumni Society Meeting of MSKCC. November 19, 1999.
235. Molecular Genetics of Solid Tumors: Determining Outcomes and Selection of Therapy. Harvard Medical School Combined Pathology Grand Rounds – Invited Professor Program. Boston, November 28-29, 1999.
236. Molecular Pathology in Cancer: Predictive Markers of Outcome and Therapy. “Francesc Duran I Reynals Symposium,” The Yale Cancer Center and Yale University School of Medicine, New Haven, December 4, 1999.
237. Molecular Determinants of Outcome and Selection of Therapy in Human Cancer. Visiting Professor’s Program, Department of Pathology, Albert Einstein College of Medicine and Montefiore Medical Center, New York, February 15, 2000.
238. Characterizing Pathways of Bladder Cancer Progression. Memorial Sloan-Kettering Cancer Center Retreat, New York, March 25, 2000.
239. Applications of Molecular Diagnostics: Solid Tumor Genetics can Determine Clinical Treatment Protocols. USCAP Long Course: Pathology in the New Millennium. USCAP 89th Annual Meeting, New Orleans, March 28, 2000.
240. Molecular Alterations Associated with Bladder Cancer Progression. Symposium on Molecular Alterations in Bladder Cancer: Translation from Bench to Bedside. 91st AACR Annual Meeting, San Francisco, April 2, 2000.
241. p53 Mutations and Inactivation of the p53 Pathway as a Predictive Clinical Determinant in Solid Tumors. 10th International p53 Workshop, Monterrey, April 6, 2000.
242. . Implicacion de la Biologia Molecular en el Pronostico de Tumores Solidos. XXV Aniversario del Servicio de Anatomia Patologica, Hospital Universitario Juan Canalejo, Coruña, Spain, May 12, 2000.
243. Premalignant Lesions and Carcinoma in Situ of the Urinary Bladder. Public Health and Clinical Significance of premalignant Alterations in the Genito-Urinary Tract, Stockholm, Sweeden, June 9, 2000.
244. Genomic Progression. Biology of Pathobiology of Cancer Workshop, Keystone, Colorado, July 20, 2000.

245. The Role of Molecular Pathology in Cancer Diagnosis and Treatment. The 2000 Danish Cancer Society Symposium, Copenhagen, Denmark, August 27-30, 2000.
246. Molecular Analysis of Adult Soft Tissue Sarcomas. Disease Management Team Presentation: Sarcoma, MSKCC, New York, September 14, 2000.
247. Keynote Speaker for "The Don Santiago Ramon y Cajal Memorial Lecture." XXIV Congress of the Spanish American Medical Dental Society, New York, October 8, 2000.
248. Molecular Pathology in Solid Tumors: Predicting Outcomes and Delivering Novel Therapeutic Strategies, Cancer Center Seminar Series, The Mount Sinai School of Medicine and the Derald H. Ruttenberg Cancer Center, New York, October 10, 2000.
249. Molecular Pathology in Oncology. Translational Research Dinner Meeting, Weil-Cornell Medical College, New York, October 19, 2000.
250. Molecular Pathology: Development of Clinical Protocols in Oncology based on Predictive Targets. Congreso Anual de Hematologia y Hemoterapia, Bilbao, Spain, October 27-29, 2000.
251. Genetic Pathways of Bladder Cancer Progression. Pathology Grand Rounds, MSKCC, New York, December 14, 2000.
252. Molecular Events in Prostate Cancer Progression. Prostate Cancer Course, MSKCC, New York, February 4, 2001.
253. Advanced Tissue Molecular Diagnostics. Special Course: Molecular Pathology 2001. 90th Annual US & Canadian Academy of Pathology Meeting, Atlanta, Marh 9, 2001.
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292. Genetic studies and molecular markers of bladder cancer. Finnish Urological Association, Winter Annual Meeting, Mikkeli, Finland, February 11-12, 2004.
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Cancer Information From CancerConsultants.com

Stage IV Renal Cancer

Overview

Patients with stage IV renal cell cancer have cancer that has spread to distant sites, invades directly into local structures or has more than one lymph node involved with cancer.

A variety of factors ultimately influence a patient's decision to receive treatment of cancer. The purpose of receiving cancer treatment may be to improve symptoms through local control of the cancer, increase a patient's chance of cure, or prolong a patient's survival. The potential benefits of receiving cancer treatment must be carefully balanced with the potential risks of receiving cancer treatment.

The following is a general overview of the treatment of stage IV renal cell cancer. Circumstances unique to your situation and prognostic factors of your cancer may ultimately influence how these general treatment principles are applied. The information on this Web site is intended to help educate you about your treatment options and to facilitate a mutual or shared decision-making process with your treating cancer physician.

Most new treatments are developed in clinical trials. Clinical trials are studies that evaluate the effectiveness of new drugs or treatment strategies. The development of more effective cancer treatments requires that new and innovative therapies be evaluated with cancer patients. Participation in a clinical trial may offer access to better treatments and advance the existing knowledge about treatment of this cancer. Clinical trials are available for most stages of cancer. Patients who are interested in participating in a clinical trial should discuss the risks and benefits of clinical trials with their physician. To ensure that you are receiving the optimal treatment of your cancer, it is important to stay informed and follow the cancer news in order to learn about new treatments and the results of clinical trials.

Patients with stage IV renal cell cancer may be offered treatment consisting of chemotherapy or biologic therapy using alpha interferon or Proleukin®; surgical removal of the cancer followed by biologic therapy or chemotherapy or participation in a clinical trial. Recent studies suggest that surgery followed by biologic therapy may yield the best results.

The surgical procedure used to treat stage IV renal cell cancer is radical nephrectomy, which involves removal of the kidney, adjacent fat and adrenal gland and any regional lymph nodes involved with cancer. Surgery is extended to include removal of all local cancer, especially when there is involvement of the renal vein and vena cava. In stage IV patients who only have local spread of renal cell cancer, surgery is performed with curative intent; however, most patients with stage IV cancer have distant metastases and local surgery is performed to prevent local complications and improve symptoms. There is a consensus that the primary cancer should be removed if possible, although there is no direct effect on distant cancer spread.

Several clinical trials have indicated that radical nephrectomy prior to treatment with interferon appears to significantly delay cancer progression and improve survival over interferon alone for patients with metastatic renal cell cancer. Recently, the *New England Journal of Medicine* reported the results of a multi-center clinical trial conducted by researchers in the Southwest Oncology Group (SWOG). The study compared treatment with surgery and interferon versus treatment with interferon alone for patients with advanced renal cell cancer. In the study, approximately 200 patients with advanced renal cell cancer were treated with either a radical nephrectomy prior to interferon treatment or interferon treatment alone. One year following treatment, 50% of patients treated with surgery and interferon were alive, compared to only 37% of patients treated with interferon only. The average duration of survival of patients that were treated with a combination of surgery and interferon was 11.1 months. For the patients treated with interferon alone, the average survival was 8.1 months. Although surgery as part of treatment for patients with advanced renal cell carcinoma has been a controversial issue, the results from this trial indicate an improvement in survival duration for patients with advanced renal cell cancer treated with surgery prior to interferon, compared with interferon alone. Using the UCLA Kidney Cancer Database, researchers identified 89 patients who met the eligibility criteria for the SWOG study and who had been treated with interleukin-2 -based regimens after undergoing nephrectomy. The survival of these patients was compared with the survival of 120 patients from the SWOG surgery-plus-interferon group. The median survival of the patients treated with nephrectomy plus interleukin-2 was 16.7 months-twice the survival in the SWOG interferon-only group and 5 months longer than that in the SWOG surgery-plus-interferon group.

Post-Surgical Treatment

Following complete or incomplete surgical removal of cancer, the majority of patients will ultimately develop cancer recurrence. This is because microscopic areas of cancer that cannot be detected persist after surgery and are responsible for causing cancer recurrence. Post-surgical treatments with chemotherapy, biologic therapy or combinations of these agents are administered to decrease the risk of cancer recurrence.

In general, biologic therapy for renal cell cancer has provided better outcomes than chemotherapy. The most active chemotherapy agents are Velban® and floxuridine. However, clinical responses to currently available single agent or combination chemotherapy do not exceed 10-15%.

Biological Modifier Therapy: Biologic response modifiers are naturally occurring or synthesized substances that direct, facilitate or enhance the body's normal immune defenses. Biologic response modifiers include interferons, interleukins, vaccines and monoclonal antibodies. In an attempt to improve survival rates, these and other agents are being tested in clinical studies.

The two most frequently used agents are Proleukin® and alfa interferon. Proleukin® works by stimulating the immune system to react against the renal cell cancer. Interferon also stimulates the immune system, thereby causing destruction of cancer cells.

Proleukin®: Proleukin® has been approved for treatment of stage IV renal cell cancer. Proleukin® has traditionally been given in high doses to patients with renal cell cancer, administered either intravenously by rapid infusion or by continuous infusion. Although high doses of Proleukin® historically have been associated with severe side effects, data analyses have demonstrated that the safety of high-dose Proleukin® has significantly improved over the past decade and the side effects are less severe.

Long-term results from a clinical trial evaluating high-dose Proleukin® in 255 patients with metastatic renal cell carcinoma have recently been reported. In this trial, 15% of patients achieved a partial or complete disappearance of their cancer following high-dose Proleukin®. The average duration of anti-cancer responses in patients who achieved a partial disappearance of cancer was 20 months. For patients who achieved a complete disappearance of cancer following treatment, the average response duration has not yet been established. Five to ten years following therapy, survival rates are approximately 10% to 20%.

Researchers have also conducted clinical trials evaluating different doses and routes of administration of Proleukin® in order to establish the optimal treatment schedule for Proleukin®. In one clinical trial, researchers from the Beth Israel Deaconess Medical Center directly compared high-dose Proleukin® to low-dose Proleukin® plus interferon. Anti-cancer response rates were 12% for patients treated with Proleukin®/interferon and 25% for patients treated with high-dose Proleukin®. Average durations of survival were 7 months for patients treated with Proleukin®/interferon and 10 months for patients treated with high-dose Proleukin®.

Alpha interferon: Interferon is a substance naturally produced in the body to help stimulate the immune system. Alpha interferon is a compound produced in a laboratory that mimics the structure and action of natural interferon. The use of interferon has yielded promising results in some types of cancer by stimulating the immune system to recognize and destroy cancer cells. However, interferon used alone as adjuvant treatment for renal cell cancer remains controversial, as side effects can be severe and no definitive conclusions regarding improved survival following treatment have been established.

Approximately 15-25% of patients with renal cell cancer will respond to various doses and schedules of alfa interferon. In general, responses occur in patients with non-bulky pulmonary and/or soft tissue renal cell cancer metastases. Responses to alpha interferon do not appear to last as long as responses to Proleukin®. Responses to alfa interferon in patients who have failed Proleukin® are poor, especially when progression has been clearly documented.

Combination Therapy

In general, attempts to add other drugs to Proleukin® regimens have been unsuccessful and the combination of alfa interferon and Proleukin® has not been associated with better results than treatment with Proleukin® alone.

Chemotherapy has been combined with Proleukin® in an attempt to improve treatment results. One multi-center trial evaluating a combination of Proleukin®, alfa interferon and retinoic acid was performed in 48 patients. Eight of 47 evaluable patients (17%) responded. Three other patients responded well enough to undergo surgery for removal of remaining cancer for an overall complete response rate of 4 out of 48, or 10%. Other clinical trials have not confirmed the effectiveness of retinoic acid treatment and clinical trials are ongoing to further evaluate this treatment.

In older or debilitated patients, it is frequently not possible to perform a radical nephrectomy, so other treatments are used to control the primary cancer. Preoperative arterial embolization is sometimes used before an operation to make surgery easier. During arterial embolization, small pieces of a special gelatin sponge or other material are injected through a catheter to clog the main renal blood vessel. This procedure shrinks the tumor by depriving it of the oxygen-carrying blood that is needed to make it grow. Arterial embolization may also be used to provide relief from pain or bleeding when removal of the cancer is not possible.

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Removal of other sites of cancer may be beneficial. Some patients can experience long-term cancer-free survival after surgical resection of metastatic cancers. These patients typically have a single or limited number of distant metastases. In some clinical studies, up to 50% of patients survived 5 years or longer after treatment of the primary cancer with radical nephrectomy and surgical removal of a solitary lung metastasis.

The combination of biologic therapy and surgery can produce long-term complete remissions in some patients with metastatic renal cell cancer. Patients who achieve a partial response to biologic therapy should be considered for surgery to produce a complete response.

Strategies to Improve Treatment

The progress that has been made in the treatment of renal cell cancer has resulted from improved surgical techniques, the development of biologic treatments and participation in clinical trials. Future progress in the treatment of renal cancer will result from continued participation in appropriate clinical trials. Currently, there are several areas of active exploration aimed at improving the treatment of renal cell cancer.

Managing Bone Complications with Bisphosphonate Drugs: Renal cell carcinoma may spread to the bone. Bone metastases may cause pain, bone loss, an increased risk of fractures, and a life-threatening condition characterized by a high level of calcium in the blood, called hypercalcemia.

Bisphosphonate drugs can effectively prevent loss of bone that occurs from metastatic lesions, reduce the risk of fractures, and decrease pain. Bisphosphonate drugs work by inhibiting bone resorption, or breakdown. Bone is constantly being "remodeled" by two types of cells: osteoclasts, which break down bone; and osteoblasts, which rebuild bone. Although the exact process by which bisphosphonates work is not completely understood, it is thought that bisphosphonates inhibit osteoclasts and induce apoptosis (cell death) in these cells, thereby reducing bone loss. There is also evidence that these drugs bind to bone, thereby blocking osteoclasts from breaking down bone. Cancer cells release various factors that stimulate osteoclastic activity, causing increased breakdown of bone. By inhibiting osteoclasts, bisphosphonate drugs effectively reduce the detrimental impact that cancer cells have on bone density.

Bisphosphonate drugs that are FDA-approved for the treatment of cancer-related skeletal complications include Zometa® (zoledronic acid) and Aredia® (pamidronate). Of these two drugs, Zometa® appears to demonstrate the strongest activity. An added benefit of Zometa® is that it is administered in a dose ten times lower than Aredia®, which considerably reduces the administration time from several hours to 15 minutes, resulting in a more convenient regimen for patients.

Researchers from Pennsylvania have reported that Zometa® improves outcomes and reduces skeletal complications in patients with renal cell carcinoma and associated bone metastases. The researchers analyzed data from 74 patients with renal cell carcinoma who were involved in a larger trial that involved patients with other types of cancers. Patients with renal cell carcinoma may be at a greater risk for developing skeletal complications than patients with other types of solid cancers. The proportion of patients with renal cell carcinoma was nearly twofold greater than the proportion of patients in the entire population (44% vs. 74%).

The patients were treated with Zometa® or placebo (inactive substitute) and compared for the

development of skeletal complications, which included bone fracture, spinal cord compression, or the need for radiation or surgery for the treatment of bone metastasis.

Patients treated with Zometa® had a 61% reduced risk of developing a skeletal complication than those who received a placebo. Also, the patients who received Zometa® had less cancer progression in their bones and lived longer.¹

To learn more about bone metastases and bone health, go to the [Bone Information Center](#)

Supportive Care: Supportive care refers to treatments designed to prevent and control the side effects of cancer and its treatment. Side effects not only cause patients discomfort, but also may prevent the optimal delivery of therapy at its planned dose and schedule. In order to achieve optimal outcomes from treatment and improve quality of life, it is imperative that side effects resulting from cancer and its treatment are appropriately managed. For more information, go to [Supportive Care](#).

New Combined Regimens: Development of new multi-agent treatment regimens that incorporate new or additional biologic and chemotherapy agents for use as treatment is an active area of clinical research carried out in phase II clinical trials. Attempts are also being made to develop regimens that combine chemotherapy with immunotherapy.

Biological Agents: Biologic agents other than Proleukin® and the interferons continue to be developed. Interleukin-12 is a relatively new interleukin that may act in part by stimulating the body to produce Interleukin-2, as well as other immune processes. In a phase I trial, one complete response was observed in 34 patients with renal cell cancer. Phase II trials are currently underway to test this drug in patients with renal cell cancer.

Proleukin®: Proleukin® is a biologic response modifier that has been approved for treatment of stage IV renal cell cancer. Clinical trials have demonstrated that approximately 15% of patients treated with high-dose Proleukin® achieve a partial or complete disappearance of their cancer. The average duration of anti-cancer responses in patients who achieved a partial disappearance of cancer is 20 months. For patients who achieved a complete disappearance of cancer following treatment, the average response duration has not yet been established. Five to ten years following therapy, survival rates are approximately 10% to 20%. These long-term anti-cancer responses and survival indicate that high-dose Proleukin® remains an extremely effective treatment option for a subset of patients with metastatic renal cell carcinoma.

Researchers have also conducted clinical trials evaluating different doses and routes of administration of Proleukin® in order to establish the optimal treatment schedule for Proleukin®. In one clinical trial, researchers from the Beth Israel Deaconess Medical Center directly compared high-dose Proleukin® to low-dose Proleukin® plus interferon. Anti-cancer response rates were 12% for patients treated with Proleukin®/interferon and 25% for patients treated with high-dose Proleukin®. Average durations of survival were 7 months for patients treated with Proleukin®/interferon and 10 months for patients treated with high-dose Proleukin®. Additional clinical trials are ongoing in an attempt to establish optimal doses and schedules coupled with the fewest side effects.

Allogeneic Stem Cell Transplant: Another way to utilize the immune system to treat cancer is by transplanting a new immune system into a patient. This is referred to as an allogeneic stem cell transplant, and immune cells (the graft) are transplanted from a healthy individual into the

patient. Prior to receiving the transplant, the patient receives high doses of chemotherapy or radiation, which "prepare" the patient to receive the donor graft. This therapy is known to cure patients with leukemia, lymphoma and other cancers. Recently, doctors at the National Heart, Lung and Blood Institute have reported the successful treatment of a patient with metastatic renal cell carcinoma using a relatively non-toxic low-dose treatment regimen to facilitate engraftment.

In addition, researchers at the National Institutes of Health (NIH) have reported a high response rate in patients with advanced renal cell cancer who received allogeneic stem cell transplants. The study involved 19 patients with metastatic renal cell cancer that was no longer responding to treatment. All patients in the study received standard-dose chemotherapy followed by an infusion of donor stem cells collected from siblings. This procedure was referred to as a mini allogeneic stem cell transplant. Patients who did not experience a regression in their cancer received additional donor white blood cell infusions to enhance the immune effect against the cancer cells. Ten patients in this study experienced a response to this treatment and three experienced a complete response. Almost 50% of patients survived beyond one year following treatment. Although a significant number of patients suffered from graft-versus-host disease, researchers are still encouraged by the high response rate, especially since these cancers were no longer responding to other treatments. Research is ongoing to determine optimal treatment strategies. To learn more, go to [Allogeneic Stem Cell Transplant](#).

Vaccines: Vaccines are substances (antigens) that specifically stimulate the immune system to react and kill the cancer cells. Vaccines are made from a variety of substances that often include the actual cancer cells removed from the patient. A difficulty in preparing vaccines is that the patient's cancer cells must be processed immediately following surgery. Therefore, patients and their surgeons must prepare in advance to ensure the removed cancer cells can be handled properly for vaccine preparation.

Vaccines are just beginning to be evaluated in a variety of cancers to see if they can produce responses to existing cancer or prevent or delay disease recurrences after treatment. In one such study, dendritic cells were incubated with renal carcinoma cells and an adjuvant KLH (keyhole limpet hemocyanine). When these cells were injected into patients, specific immunity could be detected. Clinical trials of vaccines for patients with renal cell cancer are being performed in selected cancer centers.

Gene Therapy: Gene therapy is defined as the transfer of new genetic material into a cell for therapeutic benefit. This can be accomplished by replacing or inactivating a dysfunctional gene or replacing or adding a functional gene into a cell to make to function normally. Injection of immune-enhancing cytokine genes into cancer cells has been shown to increase antigen expression at the surface of the cancer cell. This enables the immune system to recognize and attack the cancer, leading to responses to local cancers as well as distant metastases. This approach has been well tolerated and has shown some efficacy in cancer patients. Injection of Proleukin® genes directly into renal cell cancer is currently being evaluated to determine response rates.

Monoclonal Antibodies: Another approach is to deliver additional treatment directed specifically to cancer cells to avoid harming the normal cells. Some monoclonal antibodies can locate cancer cells and kill them directly. However, some antibodies have to be linked to a radioactive isotope or a toxin in order to kill cells and the antibodies essentially serve as a delivery system of the attached agents into the cell. Monoclonal antibodies can be administered alone or with chemotherapy and are being evaluated in other cancers to determine whether they can improve outcomes. Whether or not this technology can be utilized for the treatment of renal cell carcinoma

remains to be determined.

Multiple Drug Resistance Inhibitors: Renal cell carcinoma is drug resistant at the outset of treatment. Several drugs are being tested to determine if they will overcome or prevent the development of multiple drug resistance in renal cell carcinoma and other cancers.

Phase I Trials of Chemotherapy: New chemotherapeutic agents continue to be developed and evaluated in phase I clinical trials. The purpose of phase I trials is to evaluate new drugs in order to determine the best way of administering the drug and whether the drug has any anti-cancer activity in patients with renal cell cancer.

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